

University of Dundee

Effects of combined renin-angiotensin-aldosterone system inhibitor and beta-blocker treatment on outcomes in heart failure with reduced ejection fraction

Ouwerkerk, Wouter; Teng, Tiew-Hwa K.; Tromp, Jasper ; Tay, Wan Ting; Cleland, John G.; van Veldhuisen, Dirk J.

Published in:
European Journal of Heart Failure

DOI:
[10.1002/ejhf.1869](https://doi.org/10.1002/ejhf.1869)

Publication date:
2020

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Ouwerkerk, W., Teng, T-H. K., Tromp, J., Tay, W. T., Cleland, J. G., van Veldhuisen, D. J., Dickstein, K., Ng, L. L., Lang, C. C., Anker, S. D., Zannad, F., Hung, C-L., Sawhney, J. P. S., Naik, A., Shimizu, W., Hagiwara, N., Wander, G. S., Anand, I., Richards, A. M., ... Lam, C. S. P. (2020). Effects of combined renin-angiotensin-aldosterone system inhibitor and beta-blocker treatment on outcomes in heart failure with reduced ejection fraction: insights from BIOSTAT-CHF and ASIAN-HF registries. *European Journal of Heart Failure*, 22(8), 1472-1482. <https://doi.org/10.1002/ejhf.1869>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Effects of combined RAAS inhibitor and beta-blocker treatment on outcomes in heart failure with reduced ejection fraction: Insights from BIOSTAT-CHF and ASIAN-HF registries

†Wouter Ouwerkerk PhD^{1,2}, †Tiew-Hwa K Teng PhD^{1,3,4}, Jasper Tromp MD PhD^{1,4,5}, Wan Ting Tay MSc¹, John G. Cleland MD PhD⁶, Dirk J. van Veldhuisen MD PhD⁴, Kenneth Dickstein MD PhD^{7,8}, Leong L. Ng MD PhD⁹, Chim C. Lang MD PhD¹⁰, Stefan D. Anker, MD PhD¹¹, Faiez Zannad MD PhD¹², Chung-Lieh Hung MD PhD^{13,14}, J.P.S. Sawhney MD PhD¹⁵, Ajay Naik MD PhD¹⁶, Wataru Shimizu MD PhD¹⁷, Nobuhisa Hagiwara MD PhD¹⁸, Gurpreet Singh Wander MD PhD¹⁹, Inder Anand MD PhD^{20*}, A Mark Richards MD PhD^{21,22}, Adriaan A. Voors MD PhD⁴, Carolyn S.P. Lam MD PhD^{**1,4,5}

†Co-primary authors

*on behalf of the ASIAN-HF investigators, Appendix S1

** Corresponding author

1. National Heart Centre Singapore,
2. Dept of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam Infection & Immunity Institute, Amsterdam, The Netherlands
3. School of Population and Global Health, University of Western Australia, WA, Australia
4. Duke–National University of Singapore Medical School, Singapore, Singapore
5. University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, the Netherlands
6. National Heart & Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London, United Kingdom.
7. University of Bergen, Bergen, Norway
8. Stavanger University Hospital, Stavanger, Norway
9. Department of Cardiovascular Sciences, University of Leicester and NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Groby Road Leicester, LE3 9QP, United Kingdom
- 10 School of Medicine Centre for Cardiovascular and Lung Biology, Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital & Medical School, Dundee, DD1 9SY, United Kingdom
- 11 Division of Cardiology and Metabolism-Heart Failure, Cachexia & Sarcopenia; Department of Cardiology (CVK), Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité University Medicine, Charité'pl. 1, 10117 Berlin, Germany
12. Inserm CIC-P 1433, Université de Lorraine, CHRU de Nancy, FCRIN INI-CRCT, Nancy, France
- 13 Cardiovascular Division, Brigham and Women's Hospital, Boston, M, United States of America.
- 14 Division of Cardiology, Departments of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan
- 15 Sir Gangaram Hospital, New Delhi, India.
- 16 CIMS Hospital, Ahmedabad, Gujarat, India.
- 17 Department of Cardiology. Tokyo Women's Medical University 8-1 Kawada-cho, Shinjuku-ku, Tokyo
- 18 Department of Cardiovascular Medicine, Graduate School of Medicine, Nippon Medical School
- 19 Dayanand Medical College and Hospital, Ludhiana, Punjab, India
- 20 Veterans Affairs Medical Center, Minneapolis, MN, United States of America.
- 21 Cardiovascular Research Institute, National University Heart Centre, Singapore, Singapore
- 22 University of Otago, Dunedin, New Zealand

ClinicalTrials.gov Identifier: NCT01633398

Total word count: 3,022 main text (+2,399 for references and figure legends)
Abstract word count: 254

1
2 Corresponding author: Professor Carolyn S. P. Lam. MBBS, MD, PhD
3 National Heart Centre Singapore.
4 5 Hospital Dr, Singapore 169609, Singapore.
5 Tel. +65 67048965; Fax +65 68449069.
6 E-mail: carolyn.lam@duke-nus.edu.sg
7

1 **Key Points**

2 **Question:** Are better outcomes associated with lower combined doses of both ACEi/ARB and β -
3 blockers, versus the high target doses of either β -blockers or ACEi/ARBs alone, and which
4 should have priority during up-titration?

5 **Findings:** In our cohort study we found that lower dose of combined therapy was associated with
6 better outcomes than guideline recommended target doses of either monotherapy. Up-titrating β -
7 blockers was associated with a consistent and greater reduction in hazards of all-cause mortality
8 (HR for 100% GRTD: 0.40, 95% CI 0.25-0.63, compared to no treatment) than corresponding
9 ACEi/ARB up-titration (HR: 0.75, 95% CI 0.53-1.07).

10 **Meaning:** Achieving lower doses of both β -blocker and ACEi/ARB was associated with better
11 outcome than high dose of monotherapy, where up-titrating β -blockers to target dose resulted in
12 greater mortality reduction.

13

Abstract

Background. Angiotensin-converting-enzyme inhibitors (ACEi)/Angiotensin receptor blockers (ARB) and β -blockers are guideline-recommended first-line therapies in heart-failure with reduced ejection fraction (HFrEF). Previous studies showed that *individual* drug classes were under-dosed in many parts of Europe and Asia. In this study we investigated the association of *combined* up-titration of ACEi/ARBs and β -blockers on all-cause mortality and its combination with hospitalization for HF.

Methods and Results. 6,787 HFrEF patients (mean age 62.6 ± 13.2 years, 77.7% men, mean LVEF $27.7 \pm 7.2\%$) were enrolled in prospective multinational European (BIOSTAT-CHF; n=2,100) and Asian (ASIAN-HF; n= 4,687) studies. Outcomes were analysed according to achieved % guideline-recommended target doses (GRTD) of combination ACEi/ARB and β -blocker therapy, adjusted for indication bias.

Results. Only 14% (n=981) patients achieved $\geq 50\%$ GRTD for both ACEi/ARB and β -blocker. Best outcomes were observed in patients who achieved 100% GRTD of both ACEi/ARB and β -blocker (HR 0.32, 95% CI 0.26-0.39 vs. none). Lower dose of combined therapy was associated with better outcomes than 100% GRTD of either monotherapy. Up-titrating β -blockers was associated with a consistent and greater reduction in hazards of all-cause mortality (HR for 100% GRTD: 0.40, 95% CI 0.25-0.63) than corresponding ACEi/ARB up-titration (HR: 0.75, 95% CI 0.53-1.07).

1 **Conclusion.**

2 This study shows that best outcomes were observed in patients attaining GRTD for both
3 ACEi/ARB and β -blockers, unfortunately this was rarely achieved. Achieving >50% GRTD of
4 both drug classes was associated with better outcome than target dose of monotherapy. Up-
5 titrating β -blockers to target dose was associated with greater mortality reduction than up-titrating
6 ACEi/ARB.

7
8
9 **Key words:**

10 Heart failure, reduced ejection fraction, evidence-based pharmacotherapy, outcomes, up-titration

11
12 **Translational Perspective:** Our findings can inform clinical practice, particularly when
13 managing sick patients with multi-morbidity requiring polypharmacy. Best outcomes are
14 obtained with 100% GRTDs, however, under circumstances when it is challenging to up-titrate
15 both ACEi/ARB and β -blockers, achieving moderate doses of both drug classes is more
16 important than reaching maximal target doses of only one class of drug, and further up-titrating
17 β -blockers to 100% GRTD may be associated with greater mortality benefit than up-titrating
18 ACEi/ARB.

1 **Introduction**

2 Current international guidelines^{1,2} recommend up-titration of evidence-based medications
3 [angiotensin-converting enzyme-inhibitors (ACEi)/angiotensin II receptor blockers (ARB) and β -
4 blocker] in patients with heart failure and reduced ejection fraction (HFrEF) to target doses used
5 in clinical trials. The recommendations are based on evidence from large randomized clinical
6 trials that both ACEi and β -blockers, up-titrated to respective target doses, improve clinical
7 outcomes in patients with mild to moderate HFrEF^{3–13}. Furthermore, studies directly comparing
8 low versus high doses showed (trends towards) superiority of higher doses of ACEi/ARB and β -
9 blocker compared with lower doses^{14–16}. However, in daily clinical practice, patients often fail to
10 achieve guideline-recommended target doses (GRTD)^{17–21}. Patients with HF frequently have
11 multiple comorbidities and require polypharmacy, making it challenging to successfully up-titrate
12 multiple classes of HF medications²².

13 Previous studies showed that *individual* drug classes of ACEi/ARB and β -blocker were under-
14 dosed among patients with HFrEF in many parts of Europe and Asia^{20,21}. However, we did not
15 previously examine the effect of *combination* therapies on outcomes. In the current study, we
16 aimed to determine the association of *combined* up-titration of ACEi/ARB and β -blockers with
17 the first occurrence of all-cause mortality or hospitalization for HF and all-cause mortality in
18 patients with HFrEF. Specifically, we aimed to address two key questions in clinical practice:

- 19 1. Are better outcomes associated with lower combined doses of both ACEi/ARB and β -
20 blockers, versus the high target doses of either β -blockers or ACEi/ARBs alone?
- 21 2. In combination therapy of both β -blockers and ACEi/ARBs, which one (i.e. ACEi/ARB
22 or β -blocker) should have priority during up-titration?

Such practical questions are very unlikely to be answered in further large randomized controlled trials, but yet are clinically very relevant to day-to-day practice. We therefore sought to provide the best available evidence from real world data to guide these clinically important decisions.

Methods

Patient population

The design of BIoSTAT-CHF and ASIAN-HF registry have been published^{23–25}. In brief, BIoSTAT-CHF²³ enrolled 2,516 adult patients with HFrEF (left ventricular ejection fraction [LVEF] $\leq 40\%$) from 69 participating centres in 11 European countries. The ASIAN-HF registry^{24,26} is a multinational registry including 5,276 adult patients with HFrEF (LVEF $\leq 40\%$) from 46 investigation sites across 11 regions in Asia. All patients had symptoms and signs of HF and objective evidence of reduced LVEF, and were followed up for clinical outcomes of death and hospitalization. Ethics approvals were obtained from the local institutional review committee of each participating centre and all participating subjects gave informed consent. This study conforms to the ethical guidelines as laid down in the Declaration of Helsinki.

Medication and data collection

HF medications and their target doses were defined according to ESC guidelines^{1,27}. Maximum total daily doses attained during follow-up were calculated as a percentage of the guideline-recommended target daily doses (GRTD). Doses were grouped into four categories (0%, 1–49%, 50–99% and $\geq 100\%$ of GRTD per drug class, resulting in 16 possible treatment group combinations of ACEi/ARB and β -blocker. Patients were considered successfully up-titrated when $\geq 50\%$ recommended target doses for both ACEi/ARBs and β -blockers were achieved after

up-titration^{1,27}. While the use (versus non-use) of mineralocorticoid receptor antagonists (MRA) was considered, no specific MRA up-titration strategy was used in BIOSTAT-CHF or ASIAN-HF. We therefore did not include MRA dosage up-titration in our analyses, but corrected for MRA prescription.

Outcomes

The primary outcome of interest was the composite of all-cause mortality or hospitalization for HF. We also assessed all-cause mortality alone and admission to hospital because of worsening HF as secondary outcomes. Events were adjudicated by an adjudication committee in ASIAN-HF, but in BIOSTAT-CHF, adjudication was done by the treating physicians. However, a systematic meta-analysis failed to detect any effect of event adjudication on study conclusions of cardiovascular outcome trials and the numbers of events included in the final analyses were minimally changed²⁸.

Statistical analysis

We analysed data from 16 groups of patients achieving combinations of 0%, 1–49%, 50–99% and $\geq 100\%$ of GRTD of ACEi/ARB and β -blocker. In order to have enough statistical power in all 16 treatment groups, we combined both ASIAN-HF and BIOSTAT-CHF cohorts. We corrected for being included in either ASIAN-HF or BIOSTAT-CHF in all analyses. Results for each group were summarized using standard descriptive statistics including, as appropriate, mean \pm standard deviation (SD) and median plus 25th–75th percentiles or numbers and percentages. We tested differences between groups using the Kruskal-Wallis test (for contiguous variables) or the χ^2 test (for categorical variables).

1 Recognizing that both BIOSTAT-CHF and ASIAN-HF were observational non-randomized
2 studies, we were careful to adjust for treatment indication bias in outcome analysis. We used
3 three methods for adjustment: Propensity score matching, inverse probability weighting with the
4 probability to reach recommended dose and a multivariable analysis with treatment dose as
5 covariate. We only reported results of inverse probability weighting because all methods showed
6 similar results. All analyses for the effects of ACEi/ARB and β -blocker treatment were inversely
7 weighted for the probability of achieving $\geq 50\%$ GRTD^{29,30}. These weights were calculated by the
8 mean probability per patient across all imputation sets, predicted by a penalized logistic model.
9 For the penalized (LASSO) logistic regression analysis predicting successful treatment, we
10 included a comprehensive list of 41 clinical variables (Table S1). Heart rate at baseline was also
11 included in the models correcting for treatment indication bias. To prevent overfit of our
12 statistical models, we used the LASSO regression analyses to select the most parsimonious
13 model^{31,32}. All variables were normalized using Box-Cox transformations where necessary^{33,34}.
14 Missing values were imputed 5 times using multi-chain Monte Carlo methods Gibbs sampling³⁵.
15 We did 10-fold cross validation to ensure optimal penalty parameters and used all analyses for
16 each imputed dataset^{36,37}.
17 We used multivariable Cox proportional hazards regression models to examine the association of
18 percentage of GRTD prescribed (0%, 1–49%, 50–99% and $\geq 100\%$) by therapeutic class and their
19 interactions with outcome, corrected for the different cohorts. For the HF-hospitalization analysis
20 a competing risk analysis was performed with all-cause mortality as competing risk. Furthermore,
21 to investigate the differences between sex, we undertook stratified Cox proportional hazards
22 models on sex.

- 1 A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were
- 2 conducted using R, A Language and Environment for Statistical Computing, version 3.5.0 (R
- 3 Foundation for Statistical Computing, Vienna, Austria).

Results

From a total of 7,792 patients (2,516 from BIOSTAT-CHF and 5,276 from ASIAN-HF), 6,787 patients with LVEF $\leq 40\%$ and information on ACEi/ARB and β -blocker up-titration (2,100 from BIOSTAT-CHF and 4,687 from ASIAN-HF, mean age 62.6 ± 13.2 years, 77.7% men, mean LVEF $27.7 \pm 7.21\%$) were included in this analysis. Median follow-up of 2,100 patients from BIOSTAT-CHF (22 months [25th-75th percentile 17-27 months]) was similar to that in 4,687 patients from ASIAN-HF (21 [11-25] months) (Supplementary Figure S1). Patients from both cohorts were predominantly older men with a history of hypertension and ischaemic aetiology of HF; however patients from ASIAN-HF were on average ~7 years younger with lower body mass index (25 vs 28 kg/m²), less atrial fibrillation (19 vs 43%) but more diabetes (41 vs 32%) compared to those from BIOSTAT-CHF. Although there was a lower proportion of patients with severe [New York Heart Association (NYHA) class III/IV] symptoms in ASIAN-HF (34 vs 60%), more patients in ASIAN-HF had HF hospitalization within the past year compared to BIOSTAT-CHF (63 vs 32%) (Table S2). All subsequent analyses corrected for cohort.

Baseline characteristics of patients achieving the different treatment dose combinations of guideline-recommended ACEi/ARB and β -blocker target doses are presented in Table 1 (selected dose groups to illustrate characteristics of patients with predominant ACEi/ARB vs β -blocker up-titration) and Table S3 (all 16 groups of dose combinations of the two drug classes). As expected, compared to patients not receiving the drug or receiving only low doses, patients who achieved higher doses were younger, had higher blood pressure and better renal function (for ACEi/ARB up-titration) at baseline, and were more likely to have a history of hypertension or myocardial infarction but less likely to have a history of chronic obstructive pulmonary disease (for β -blocker up-titration). Among the 41 clinical variables included in multivariable models, country of

origin/enrolment, **younger** age, higher systolic/diastolic blood pressure, hypertension, current smoking and history of myocardial infarction were significant independent predictors which were positively associated with attainment of $\geq 50\%$ GRTD for either therapeutic class. In contrast, the presence of peripheral oedema, higher NYHA class, chronic obstructive pulmonary disease and increasing serum creatinine levels were negatively associated with attainment of GRTDs (Table S4). **This model had an AUC of 0.72 and 0.71 when correcting for optimism.**

Of the 6,787 patients, only 14% (n= 981) patients achieved $\geq 50\%$ GRTD and 3% (n=190) achieved 100% GRTD for both ACEi/ARB and β -blocker (Table 2). The majority (52%) of patients only achieved 1-49% of the GRTD of β -blockers, regardless of ACEi/ARB, with little heterogeneity between BIOSTAT-CHF and ASIAN-HF sub-cohorts (Figure 1).

Association of achieved dose (0%, 1-49%, 50-99% and $\geq 100\%$) with all-cause mortality or heart failure-related hospitalization

After adjusting for indication bias and correcting for cohorts, increasing doses towards recommended ACEi/ARB and β -blocker doses were generally associated with a decreasing risk of a composite outcome (mortality or heart failure hospitalization), Figure 2a. When any dose (up to 49% GRTD) was given for both ACEi/ARB and β -blocker, the hazard of composite outcome was lower (Hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.61-0.84) compared with none (Table 2). Increasing the doses further to 50-99% GRTD for either ACEi/ARB or β -blocker in combination therapy reduced the hazards markedly (HR 0.50/0.61). Of note, the reduction in hazards observed for these combinations, even though not reaching 100% GRTD in either drug class, was greater than that observed with the attainment of 100% GRTD for ACEi/ARB alone (HR 0.71, 95% CI 0.52-0.96) or 100% GRTD for β -blocker alone (HR 0.68, 95% CI 0.49-

0.93)(Table 2). Treating patients at sub-optimal ACE/ARB and BB doses (1-49% of GDMT) appears not to be better than treating patients at high dose of either single therapy. However, as soon as one of the treatment doses is increased to at least 50% of guideline dose, the risks reduce to 0.61 (95% CI 0.49-0.75) and 0.50 (95% CI 0.42-0.61) which is lower than 0.67 and 0.71 for the groups with <50% GDMT. Achievement of 100% of recommended doses for ACEi/ARB and β -blockers was associated with the lowest hazard ratios (HR 0.32 CI 0.26-0.39). Correcting for MRA prescription did not alter the risks of the separate treatment groups. Sex modified the association of medication doses with composite outcomes ($p=0.001$). In stratified analyses, for all outcomes, women benefited more at lower doses than men, even with sub-optimal doses of <50% GRTD (supplementary table S5).

Association of achieved dose (0%, 1-49%, 50-99% and $\geq 100\%$) with all-cause mortality

Compared to patients not treated with ACEi/ARB and β -blockers, the lowest risk in all-cause mortality was observed in those achieving 100% GRTD for both therapeutic classes (with HR 0.19, 95% CI 0.14-0.24, Table 2, Figure 2b). The second lowest risk HR 0.27 (95% CI 0.21-0.34) was among those with 50-99% target dose for ACEi/ARB and 100% target dose for β -blockers. As monotherapy, achievement of 100% GRTD for ACEi/ARB was not associated with additional mortality benefit compared to lower doses of ACEi/ARB; in contrast, increasing doses of β -blockers as monotherapy was associated with steady reduction in hazards for mortality (from HR 0.75 [95% CI 0.6-0.92] with 1-49% GRTD, to 0.65 [95% CI, 0.48-0.87] with 50-99% GRTD, to 0.4 [95% CI 0.25-0.63] with 100% GRTD).

Association of achieved dose (0%, 1-49%, 50-99% and $\geq 100\%$) with HF-related hospitalization

Increasing doses of combinations of ACE-inhibitors/ARBs and β -blockers were not directly associated with risk of HF-hospitalization (Table 2, Figure 2c), although a lower risk was seen in patients with increasing dose of single therapy of ACE-inhibitors/ARBs.

Discussion

Our key findings from our multinational observational studies are: In both Europe and Asia, achievement of full GRTD for both ACEi/ARB and β -blockers was rare. Not surprisingly, the best outcomes were observed in those who achieved 100% GRTD of combined therapy. However, in the vast majority of patients not reaching 100% GRTD, taking any dose combination was better than none, and achieving lower doses of both drug classes was associated with better outcomes than reaching the highest dose of only one class. For mortality reduction, up-titrating β -blockers to 100% GRTD was associated with greater benefit than up-titrating ACEi/ARB to 100% GRTD. The key practical questions we sought to answer in this study are very unlikely to be answered in large randomized controlled trials, yet very relevant to day-to-day clinical practice. In RCTs, novel drugs are given on top of standard of care. However, regarding standard of care, the main outcome papers of these RCTs only provide data on whether ACEi/ARB/BB/MRA etc are used or not (yes/no) but the doses as percentage of the guideline-recommended target doses are never reported. In this paper these data are provided which makes them even more important.

There are few previous reports on the doses of first-line evidence-based pharmacotherapy in HFrEF patients^{20,21,38-40}. Despite robust evidence showing the benefits of attainment of GRTD of ACEi/ARB^{14,16} and β -blockers^{15,41,42}, many studies report failure to achieve guideline-target

doses in usual care setting^{20,21,38,39,43,44}, and even in the trial setting, with CIBIS-II¹⁰, CIBIS-ELD⁴⁵ and HF-ACTION⁴⁶ showing that $\leq 25\%$ to $\leq 50\%$, of patients achieve target doses of β -blockers⁴². Reasons for failure to achieve guideline-targeted doses are multifactorial and include patients' clinical status, drug intolerance or adverse effects (for instance hypotension, bradycardia, renal impairment, hyperkalaemia, and other real or perceived side effects), physicians' prescribing patterns, polypharmacy and lack of compliance, as well as cost constraints⁴⁷. Our results are consistent with contemporary US-based data, with the recently reported CHAMP-HF (Change the Management of Patients with Heart Failure) registry^{38,39} showing that $<20\%$ of eligible patients were receiving target doses of ACEi/ARBs and β -blockers, even among those with systolic blood pressure ≥ 110 mm Hg, and a remarkably low 1% of patients receiving target doses of ACEi/ARBs, β -blockers and MRAs. The CHAMP-HF registry also systematically analysed reasons for lack of up-titration of medications and found that among those who were treated with ACEi/ARBs, higher systolic blood pressure and a history of hypertension (for ACEi/ARBs), black race, and obesity/diabetes (for β -blockers) were associated with achieving target doses; whereas prior HF hospitalization within 12 months, asthma/ chronic obstructive pulmonary disease, and NYHA functional class III/IV status were associated with sub-target doses. For all-cause mortality, graduated decreases in relative risk of deaths with increasing doses of ACEi/ARBs and beta-blockers were observed (Figure 2b). In contrast, the association of high doses of medications observed in HFH (Figure 2c), could potentially stem from other non-medical factors, e.g. limited access to care; differences in health care systems across geography, particularly in regard to coordinated primary care following discharge; variation in delivery and quality of cardiac care, and others as reported in the QUALIFY international registry⁴⁸⁻⁵⁰.

1 In light of the known challenges in day-to-day practice of achieving 100% target doses of
2 combination therapies in HFrEF, our results emphasize that “some is better than none”. These
3 results add to that of studies in the SOLVD and CIBIS II trials, which showed the effects of low
4 dose enalapril⁵¹ or bisoprolol⁵² as single therapy. The TRED-HF trial⁵³ showed that withdrawal
5 of treatment studied the effect of evidence-based medical treatment withdrawal. All studies show
6 that patients already benefit from small doses of guideline-directed medical therapies. Thus,
7 initiating and maintaining guideline-directed medical therapies in patients with HFrEF remains a
8 quintessential aim in the management of these patients, even when target dose is not reached.

9
10 However, how do we manage dose titration in cases where full target doses of combination drugs
11 cannot be achieved (for instance when blood pressure is borderline)? Our results suggest that up-
12 titration to even sub-target doses of both ACEi/ARBs and β -blockers was associated with better
13 outcomes than full up-titration to 100% target doses of a single drug class (with either none or
14 very low doses of the other drug class). This is not to say that attempts at up-titration are not
15 important in real world practice; on the contrary we showed that achievement of higher doses of
16 both guideline-recommended drug classes was associated with reduction in composite outcomes
17 of death and HF hospitalization, consistent with prior trial evidence comparing lower versus
18 higher doses of guideline-directed medical therapies. In the ATLAS trial¹⁴, treatment with high
19 (32.5 to 35mg) vs low (2.5 to 5mg) daily doses lisinopril was associated with a non-significant
20 8% lower hazard of death but a significant 12% lower risk of all-cause death or hospitalization,
21 and 24% fewer hospitalizations for HF. Similar findings were found in the HEAAL trial, with the
22 use of low dose (50mg) vs. high dose (150mg) losartan¹⁶. In both trials, symptomatic
23 hypotension/syncope and renal insufficiency, and hyperkalaemia (only in HEAAL trial), were

more prevalent in the high dose group. The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial⁵⁴ was undertaken to establish the efficacy and safety of two doses (low-5mg/day; high-20mg/day) of long-term carvedilol vs. placebo, in Japanese patients with HF and LVEF $\leq 40\%$. There was no statistical difference in outcomes between the high and low dose of carvedilol. High (≥ 25 mg/day) vs. low dose (< 25 mg/day) carvedilol equivalents in HF-ACTION also conferred similar benefit for all-cause mortality and CV outcomes, although high dose was superior (albeit with marginal significance) for a composite outcome of all-cause mortality or HF hospitalization^{38,39}. Our results build on these prior trials and suggest that when faced with the clinical conundrum of up-titrating both drugs versus up-titrating only one of the drugs to maximal target doses, the former may be a preferable approach. Furthermore, we observed that up-titrating β -blockers to 100% GRTD was associated with mortality benefit, even when doses of ACEi/ARB were still sub-target. As a cautionary note, the guidelines advised slow up-titration of β -blockers due to a possible transient HF worsening during the first 2 weeks after upstart with β -blockers.

This contemporary prospective multinational study spans a huge geography in Europe and Asia. Both studies were designed with a specific investigator-directed question regarding reasons for not achieving recommended doses; however, in a large proportion of cases there was a lack of further specification of the reason for not achieving GRTD other than 'unknown'. Specific contraindications to further up-titration of medications were not captured, although those with absolute contraindications to ACEi/ARBs at baseline remained small. The impact of incident renal failure on discontinuation of treatment could not be examined.

Robust statistical analytical methods were used and we corrected for indication bias; unfortunately, if this correction was sufficient is untestable and there remains potential for residual bias. We further acknowledge that lack of persistence and adherence to medications may play a role, but cannot be directly measured in our study. We were unable to assess the change in heart rate with up-titration of β -blockers. While concurrent use of MRAs were accounted for (vs non-use), we did not assess different doses of MRAs. Nonetheless, our observation ‘real world’ data from large cohorts may provide the best available evidence to guide clinically important decisions which are unlikely to be tested in future large randomized controlled trials.

Conclusions

Our multinational real-world data suggest that although best outcomes were observed in patients attaining 100% GRTD for both ACEi/ARB and β -blockers, such combined maximal up-titration was rarely achieved. Achieving lower doses of both drug classes to at least 50% GRTD was associated with better outcomes than reaching the target dose of only one class; and further up-titrating β -blockers to 100% GRTD was associated with greater mortality benefit than up-titrating ACEi/ARB. Our data suggest that less is better than nothing, but since this is not a randomized controlled trial, no strong recommendations can be made. The only recommendation that can be made is that ACEi/ARB and beta-blockers should be uptitrated to the recommended doses as stated in all heart failure guidelines.

Acknowledgements

The contribution of all site investigators and clinical coordinators are duly acknowledged

Funding

This work was supported by a grant from the European Commission [FP7-242209-BIOSTAT-CHF; EudraCT 2010-020808-29]

The ASIAN-HF is supported by research grants from Boston Scientific Investigator Sponsored Research Program, National Medical Research Council of Singapore (R-172-003-219-511), A*STAR Biomedical Research Council Asian neTwork for Translational Research and Cardiovascular Trials (ATTRaCT) program (SPF2014/003, SPF2014/004, SPF2014/005), and Bayer.

Declaration of interests (alphabetical order):

CSL is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, WebMD Global LLC, Radcliffe Group Ltd and Corpus.

AAV received grants from European Commission; personal fees from Amgen, Boehringer Ingelheim, AstraZeneca, Bayer, Cytokinetics, GSK, Myokardia, Novartis, Servier, grants and personal fees from Roche diagnostics.

Metra received consulting honoraria from Amgen, Bayer, Novartis, Servier

1 Anker reports consultancy for Thermo Fisher, and Consultancy and Research Support from Vifor
2 Pharma
3 Filippatos received fees and/ or research grants from Novartis, Bayer, Cardioventis, Vifor,
4 Servier, Alere, Abbott
5 AMR has received research support from Boston Scientific, Bayer, Astra Zeneca, Medtronic,
6 Roche Diagnostics, Abbott Laboratories, Thermo Fisher, Critical Diagnostics and has consulted
7 for Bayer, Novartis, Merck, Astra Zeneca, Roche Diagnostics.

1 APPENDIX I

2 The ASIAN-HF investigators author block

3 THE ASIAN-HF EXECUTIVE COMMITTEE

- 4• Professor A. Mark Richards (as Chairman), Cardiovascular Research Institute, National
5 University of Singapore, Singapore. Email: mdcarthu@nus.edu.sg
- 6• Professor Carolyn S.P. Lam (as Principal Investigator), National Heart Centre Singapore, Duke-
7 NUS Medical School, Singapore. Email: carolyn.lam@duke-nus.edu.sg
- 8• Professor Inder Anand (as Director, Publications Committee), University of Minnesota Medical
9 School, VA Medical Center Minneapolis and San Diego, United States of America. Email:
10 anand001@umn.edu
- 11• Dr Chung-Lieh Hung, Mackay Memorial Hospital, Taipei, Taiwan. Email:
12 jotaro3791@gmail.com
- 13• Professor Lieng Hsi Ling (as Director, Echo Core Laboratory), Cardiovascular Research Institute,
14 National University of Singapore, Singapore. Email: lieng_hsi_ling@nuhs.edu.sg
- 15• Dr Hounq Bang Liew, Queen Elizabeth II Hospital, Clinical Research Center, Sabah, Malaysia.
16 Email: hbliew22@gmail.com
- 17• Dr Calambur Narasimhan, Care Hospital, Hyderabad, India. Email: calambur@hotmail.com
- 18• Dr Tachapong Ngarmukos, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.
19 Email: tachaponis.nga@mahidol.ac.th
- 20• Dr Sang Weon Park, SeJong General Hospital, Seoul, South Korea. Email:
21 swparkmd@gmail.com
- 22• Dr Eugenio Reyes, Manila Doctors Hospital, Manila, Philippines. Email:
23 eugenereyes@yahoo.com
- 24• Professor Bambang B. Siswanto, National Cardiovascular Center Universitas Indonesia, Jakarta,
25 Indonesia. Email: bambbs@gmail.com
- 26• Professor Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School,
27 Tokyo, Japan. Email: wshimizu@nms.ac.jp
- 28• Professor Shu Zhang, Fuwai Cardiovascular Hospital, Beijing, People's Republic of China.
29 Email: zsfuwai@vip.163.com

30

31 COUNTRY AND SITE INVESTIGATORS

- 32 China
- 33 Fuwai Hospital: **Shu Zhang** (Country PI), Xiaohan Fan, Keping Chen. Ruijin Hospital, Shanghai
- 34 Jiaotong university: Liqun Wu, Yucai Xie, Qi Jin, Tianyou Ling. The First Affiliated Hospital
- 35 With Nanjing Medical University: Xinli Li, Fang Zhou, Yanli Zhou, Dongjie Xu, Haifeng Zhang.

Zhongshan Hospital Fudan University: Yangang Su, Xueying Chen, Shengmei Qin, Jingfeng Wang, Xue Gong, Zhaodi Wu.

Hong Kong
The Chinese University of Hong Kong: **Cheuk Man Yu** (Country PI).

India
CARE Hospital: **Calambur Narasimhan** (Country PI), B K S Sastry, Arun Gopi, K Raghu, C Sridevi, Daljeet Kaur. Care Institute of Medical Sciences: Ajay Naik, Keyur Parikh, Anish Chandarana, Urmil Shah, Milan Chag, Hemang Baxi, Satya Gupta, Jyoti Bhatia, Vaishali Khakhkhar, Vineet Sankhla, Tejas Patel, Vipul Kapoor. Hero Dayanand Medical College Heart Institute: Gurpreet Singh Wander, Rohit Tandon. Medanta-The Medicity: Vijay Chopra, Manoj Kumar, Hatinder Jeet Singh Sethi, Rashmi Verma, Sanjay Mittal. Sir Ganga Ram Hospital: Jitendra Sawhney, Manish Kr. Sharma. Westfort Hi-Tech Hospital Ltd: Mohanan Padinhare Purayil.

Indonesia
Rumah Sakit Jantung dan Pembuluh Darah Harapan Kita: **Bambang Budi Siswanto** (Country PI). RS Dr Hasan Sadikin: Pintoko Tedjokusumo, Erwan Martanto, Erwinanto. R S Khusus Jantung Binawaluya: Muhammad Munawar, Jimmy Agung Pambudi. RS Siloam Karawaci: Antonia Lukito, Ingrid Pardede, Alvin Thengker, Vito Damay, Siska Suridanda Danny, Rarsari Surarso.

Japan
Nippon Medical School: **Wataru Shimizu** (Country PI), National Cerebral and Cardiovascular Center: Takashi Noda, Ikutaro Nakajima, Mitsuru Wada, Kohei Ishibashi. Kinki University Hospital Cardiovascular Center: Takashi Kurita, Ryoubun Yasuoka. Nippon Medical School Hospital: Kuniya Asai, Kohji Murai, Yoshiaki Kubota, Yuki Izumi. Toho University Omori Medical Center: Takanori Ikeda, Shinji Hisatake, Takayuki Kabuki, Shunsuke Kiuchi, Tokyo Women's Medical University: Nobuhisa Hagiwara, Atsushi Suzuki, Dr. Tsuyoshi Suzuki.

Korea
SeJong General Hospital: **Sang-Weon Park** (Country PI), Suk Keun Hong, SookJin Lee, Lim Dal Soo, Dong-Hyeok Kim. Korea University Anam Hospital: Jaemin Shim, Seong-Mi Park, Seung-Young Roh, Young Hoon Kim, Mina Kim, Jong-Il Choi. Korea University Guro Hospital: Jin Oh Na, Seung Woon Rha, Hong Seog Seo, Dong Joo Oh, Chang Gyu Park, Eung Ju Kim, Sunki Lee, Severance Hospital, Yonsei University Health System: Boyoung Joung, Jae-Sun Uhm, Moon Hyoung Lee, In-Jeong Cho, Hui-Nam Park. Chonnam National University Hospital: Hyung-Wook Park, Jeong-Gwan Cho, Namsik Yoon, KiHong Lee, Kye Hun Kim. Korea University Ansan Hospital: Seong Hwan Kim.

Malaysia
Hospital Queen Elizabeth II: **Houng Bang Liew** (Country PI), Sahrin Saharudin, Boon Cong Beh, Yu Wei Lee, Chia How Yen, Mohd Khairi Othman, Amie-Anne Augustine, Mohd Hariz

1 Mohd Asnawi, Roberto Angelo Mojolou, You Zhuan Tan, Aida Nurbaini Arbain, Chii Koh
2 Wong. Institut Jantung Negara: Razali Omar, Azmee Mohd Ghazi, Surinder Kaur Khelae, David
3 S.P. Chew, Lok Bin Yap, Azlan Hussin, Zulkeflee Muhammad, Mohd. Ghazi Azmee. University
4 Malaya Medical Centre: Imran Zainal Abidin, Ahmad Syadi Bin Mahmood Zhudi, Nor Ashikin
5 Md Sari, Ganiga Srinivasaiah Sridhar, Ahmad Syadi Mahmood Zuhdi. Muhammad Dzafir Ismail.
6 Sarawak General Hospital Heart Centre: Tiong Kiam Ong, Yee Ling Cham, Ning Zan Khiew,
7 Asri Bin Said, Alan Yean Yip Fong, Nor Hanim Mohd Amin, Keong Chua Seng, Sian Kong Tan,
8 Kuan Leong Yew.

9
10 Philippines

11 Manila Doctors Hospital: **Eugenio Reyes** (Country PI), Jones Santos, Allan Lim. Makati Medical
12 Center: Raul Lapitan, Ryan Andal, Philippine Heart Center: Eleanor Lopez.

13
14 Singapore

15 National Heart Centre Singapore: **Carolyn S.P. Lam** (Country PI), A. Mark Richards, Kheng
16 Leng David Sim, Boon Yew Tan, Choon Pin Lim, Louis L.Y. Teo, Laura L.H. Chan. National
17 University Heart Centre: Lieng Hsi Ling, Ping Chai, Ching Chiew Raymond Wong, Kian Keong
18 Poh, Tan Tock Seng Hospital: Poh Shuan Daniel Yeo, Evelyn M. Lee, Seet Yong Loh, Min Er
19 Ching, Deanna Z.L. Khoo, Min Sen Yew, Wenjie Huang. Changi General Hospital-Parent: Kui
20 Toh Gerard Leong, Jia Hao Jason See, Yaozong Benji Lim, Svenszeat Tan, Colin Yeo, Siang
21 Chew Chai. Singapore General Hospital-Parent: Fazlur Rehman Jaufeerally, Haresh Tulsidas,
22 Than Aung. Khoo Teck Puat Hospital: Hean Yee Ong, Lee Fong Ling, Dinna Kar Nee Soon

23
24 Taiwan

25 Mackay Memorial Hospital, Taipei, Taiwan: **Chung-Lieh Hung** (Country PI), Hung-I Yeh, Jen-
26 Yuan Kuo, Chih-Hsuan Yen. National Taiwan University Hospital: Juey-Jen Hwang, Kuo-Liong
27 Chien, Ta-Chen Su, Lian-Yu Lin, Jyh-Ming Juang, Yen-Hung Lin, Fu-Tien Chiang, Jiunn-Lee
28 Lin, Yi-Lwun Ho, Chii-Ming Lee, Po-Chih Lin, Chi-Sheng Hung, Sheng-Nan Chang, Jou-Wei
29 Lin, Chih-Neng Hsu. Taipei Veterans General Hospital: Wen-Chung Yu, Tze-Fan Chao, Shih-
30 Hsien Sung, Kang-Ling Wang, Hsin-Bang Leu, Yenn-Jiang Lin, Shih-Lin Chang, Po-Hsun
31 Huang, Li-Wei Lo, Cheng-Hsueh Wu. China Medical University Hospital: Hsin-Yueh Liang,
32 Shih-Sheng Chang, Lien-Cheng Hsiao, Yu-Chen Wang, Chiung-Ray Lu, Hung-Pin Wu, Yen-
33 Nien Lin, Ke-Wei Chen, Ping-Han Lo, Chung-Ho Hsu, Li-Chuan Hsieh.

34
35 Thailand

36 Ramathibodi Hospital: **Tachapong Ngarmukos** (Country PI), Mann Chandavimol, Teerapat
37 Yingchoncharoen, Prasart Laothavorn. Phramongkutklo Hospital: Waraporn Tiyanon. Maharaj
38 Nakorn Chiang Mai Hospital: Wanwarang Wongcharoen, Arintaya Phrommintikul.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meer P van der, Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *Eur J Heart Fail* 2016;**18**:891–975.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of Amer. *Circulation* 2017;**136**:252–289.
3. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
4. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995;**273**:1450–1456.
5. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB,

- Loeb H, Wong M. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;**325**:303–310.
6. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**:1349–1355.
 7. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, Allaf D El, Vítovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;**283**:1295–1302.
 8. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651–1658.
 9. Poole-Wilson P a, Swedberg K, Cleland JGF, Lenarda A Di, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A, Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet (London, England)* 2003;**362**:7–13.
 10. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II

- (CIBIS-II): a randomised trial. *Lancet (London, England)* 1999;**353**:9–13.
11. Flather MD, Shibata MC, Coats AJS, Veldhuisen DJ Van, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Böhm M, Anker SD, Thompson SG, Poole-Wilson PA, SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–225.
 12. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–1435.
 13. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;**327**:685–691.
 14. Packer M, Poole-Wilson P a., Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999;**100**:2312–2318.
 15. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996;**94**:2807–2816.
 16. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GAJ, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA, HEAAL Investigators. Effects

of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet (London, England)* Elsevier Ltd; 2009;**374**:1840–1848.

17. Cleland JGF. Contemporary management of heart failure in clinical practice. *Heart* 2002;**88 Suppl 2**:ii5-8.
18. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, Dietz R, Gavazzi A, Gilst WH Van, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, Widimsky J, Freemantle N, Eastaugh J, Mason J, Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J* 2003;**24**:464–474.
19. Kalra PR, Morley C, Barnes S, Menown I, Kassianos G, Padmanabhan S, Gupta S, Lang CC. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. *Int J Cardiol* Elsevier Ireland Ltd; 2013;**167**:2695–2699.
20. Teng T-HK, Tromp J, Tay WT, Anand I, Ouwerkerk W, Chopra V, Wander GS, Yap JJ, MacDonald MR, Xu CF, Chia YM, Shimizu W, ASIAN-HF investigators, Richards AM, Voors A, Lam CS. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study. *Lancet Glob Heal* The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND 4.0 license; 2018;**6**:e1008–e1018.
21. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, Harst P Van Der, Hillege HL, Lang CC, Maaten JM Ter, Ng LL, Ponikowski P, Samani NJ, Veldhuisen DJ Van, Zannad F, Metra M, Zwinderman AH. Determinants and clinical outcome of

- uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: A prospective European study. *Eur Heart J* 2017;**38**:1883–1890.
22. DeVore AD, Thomas L, Albert NM, Butler J, Hernandez AF, Patterson JH, Spertus JA, Williams FB, Turner SJ, Chan WW, Duffy CI, McCague K, Mi X, Fonarow GC. Change the management of patients with heart failure: Rationale and design of the CHAMP-HF registry. *Am Heart J* Elsevier Inc.; 2017;**189**:177–183.
 23. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, Harst P van der, Hillege HL, Lang CC, Maaten JM Ter, Ng L, Ponikowski P, Samani NJ, Veldhuisen DJ van, Zannad F, Zwinderman AH, Metra M. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur J Heart Fail* 2016;**18**:716–726.
 24. Lam CSP, Teng THK, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto AB, Hung CL, Ling LH, Yap J, MacDonald M, Richards AM. Regional and ethnic differences among patients with heart failure in Asia: The Asian sudden cardiac death in heart failure registry. *Eur Heart J* 2016;**37**:3141–3153.
 25. Lam CSP, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto B, Ling LH, Richards AM. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. *Eur J Heart Fail* 2013;**15**:928–936.
 26. Tromp J, Tay WT, Ouwerkerk W, Teng T-HK, Yap J, MacDonald MR, Leineweber K, McMurray JJ V., Zile MR, Anand IS, Lam CSP. Multimorbidity in patients with heart failure from 11 Asian regions: A prospective cohort study using the ASIAN-HF registry. Rahimi K, ed. *PLOS Med* 2018;**15**:e1002541.

27. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ V, Ponikowski P, Poole-Wilson PA, Strömberg A, Veldhuisen DJ van, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart. *Eur Heart J* 2008;**29**:2388–2442.
28. Pogue J, Walter SD, Yusuf S. Evaluating the benefit of event adjudication of cardiovascular outcomes in large simple RCTs. *Clin Trials* 2009;**6**:239–251.
29. Wal WM van der, Geskus RB. ipw : An R Package for Inverse Probability Weighting. *J Stat Softw* 2011;**43**:1–22.
30. Halloran ME, Berry D, eds. Statistical Models in Epidemiology, the Environment, and Clinical Trials. New York, NY: Springer New York; 2000.
31. McNeish DM. Using Lasso for Predictor Selection and to Assuage Overfitting: A Method Long Overlooked in Behavioral Sciences. *Multivariate Behav Res* 2015;**50**:471–484.
32. Tibshirani R. The lasso method for variable selection in the Cox model. *Stat Med* 1997;**16**:385–395.
33. Box GEP, Cox DR. An Analysis of Transformations Revisited, Rebutted. *J Am Stat Assoc* 1982;**77**:209.
34. Clark JE, Osborne JW, Gallagher P, Watson S. A simple method for optimising transformation of non-parametric data: an illustration by reference to cortisol assays. *Hum Psychopharmacol* 2016;**31**:259–267.
35. Buuren S van, Groothuis-Oudshoorn K. mice : Multivariate Imputation by Chained

- Equations in R. *J Stat Softw* 2011;**45**:1–67.
36. Hastie T, Tibshirani R, Friedman J. The Elements of Statistical Learning. New York, NY: Springer New York; 2009.
 37. Zou H, Hastie T. Regularization and variable selection via the elastic net. *J R Stat Soc Ser B (Statistical Methodol)* 2005;**67**:301–320.
 38. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Fonarow GC. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. *J Am Coll Cardiol* 2018;**72**:351–366.
 39. Peri-Okonny PA, Mi X, Khariton Y, Patel KK, Thomas L, Fonarow GC, Sharma PP, Duffy CI, Albert NM, Butler J, Hernandez AF, McCague K, Williams FB, DeVore AD, Patterson JH, Spertus JA. Target Doses of Heart Failure Medical Therapy and Blood Pressure: Insights From the CHAMP-HF Registry. *JACC Heart Fail* 2019;**7**:350–358.
 40. Heywood JT, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Gheorghiade M, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN. Comparison of medical therapy dosing in outpatients cared for in cardiology practices with heart failure and reduced ejection fraction with and without device therapy: report from IMPROVE HF. *Circ Heart Fail* 2010;**3**:596–605.
 41. Fiuzat M, Wojdyla D, Kitzman D, Fleg J, Keteyian SJ, Kraus WE, Piña IL, Whellan D, O'Connor CM. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *J Am Coll Cardiol* 2012;**60**:208–215.

42. Bhatt AS, DeVore AD, DeWald TA, Swedberg K, Mentz RJ. Achieving a Maximally Tolerated β -Blocker Dose in Heart Failure Patients: Is There Room for Improvement? *J Am Coll Cardiol* 2017;**69**:2542–2550.
43. DeVore AD, Mi X, Mentz RJ, Fonarow GC, Dyke MK Van, Maya JF, Hardy NC, Hammill BG, Hernandez AF. Discharge heart rate and β -blocker dose in patients hospitalized with heart failure: Findings from the OPTIMIZE-HF registry. *Am Heart J* Elsevier B.V.; 2016;**173**:172–178.
44. Fowler MB, Lottes SR, Nelson JJ, Lukas MA, Gilbert EM, Greenberg B, Massie BM, Abraham WT, Franciosa JA, COHERE Participant Physicians. Beta-blocker dosing in community-based treatment of heart failure. *Am Heart J* 2007;**153**:1029–1036.
45. Düngen H-D, Apostolovic S, Inkrot S, Tahirovic E, Töpper A, Mehrhof F, Prettin C, Putnikovic B, Neskovic AN, Krotin M, Sakac D, Lainscak M, Edelmann F, Wachter R, Rau T, Eschenhagen T, Doehner W, Anker SD, Waagstein F, Herrmann-Lingen C, Gelbrich G, Dietz R, CIBIS-ELD investigators and Project Multicentre Trials in the Competence Network Heart Failure. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. *Eur J Heart Fail* 2011;**13**:670–680.
46. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL, HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
47. Bozkurt B. Reasons for Lack of Improvement in Treatment With Evidence-Based

Therapies in Heart Failure. *J Am Coll Cardiol* 2019;**73**:2384–2387.

48. Komajda M, Anker SD, Cowie MR, Filippatos GS, Mengelle B, Ponikowski P, Tavazzi L, QUALIFY Investigators. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. *Eur J Heart Fail* 2016;**18**:514–522.
49. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS, QUALIFY Investigators. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017;**19**:1414–1423.
50. Komajda M, Schöpe J, Wagenpfeil S, Tavazzi L, Böhm M, Ponikowski P, Anker SD, Filippatos GS, Cowie MR, QUALIFY Investigators. Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2019;**21**:921–929.
51. Lam PH, Dooley DJ, Fonarow GC, Butler J, Bhatt DL, Filippatos GS, Deedwania P, Forman DE, White M, Fletcher RD, Arundel C, Blackman MR, Adamopoulos C, Kanonidis IE, Aban IB, Patel K, Aronow WS, Allman RM, Anker SD, Pitt B, Ahmed A. Similar clinical benefits from below-target and target dose enalapril in patients with heart failure in the SOLVD Treatment trial. *Eur J Heart Fail* 2018;**20**:359–369.
52. Simon T, Mary-Krause M, Funck-Brentano C, Lechat P, Jaillon P. Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study(CIBIS II). *Eur Heart J* 2003;**24**:552–559.
53. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R,

Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JGF, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license; 2019;**393**:61–73.

54. Hori M, Sasayama S, Kitabatake A, Toyooka T, Handa S, Yokoyama M, Matsuzaki M, Takeshita A, Origasa H, Matsui K, Hosoda S, MUCHA Investigators. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. *Am Heart J* 2004;**147**:324–330.

Figure legends

Figure 1: Distribution of ACEi/ARB and β -blocker in ASIAN-HF and BIOSAT-CHF

Figure 2 A: Hazard Ratio of mortality and/or HF-related hospitalization for patients achieving a combination of 0, 1-49, 50-99% and $\geq 100\%$ recommended treatment dose of ACEi/ARB and β -blocker dose; **B:** Hazard Ratio of mortality for patients achieving a combination of 0, 1-49, 50-99% and $\geq 100\%$ recommended treatment dose of ACEi/ARB and β -blocker dose; **C:** Hazard Ratio of HF-related hospitalization for patients achieving a combination of 0, 1-49, 50-99% and $\geq 100\%$ recommended treatment dose of ACEi/ARB and β -blocker dose;

Table 1: Baseline characteristics of patients achieving low dose, high dose and target dose of guideline recommended treatment

| Variable | All | A0B0 | A0B1 | A0B2 | A0B3 | P for trend B1 to B3 (A0) | A1B0 | A2B0 | A3B0 | P for trend A1 to A3 (B0) | Other |
|--|-----------------|--------------|---------------|--------------|------------------|---------------------------------|------------------|--------------|------------------|---------------------------------|---------------|
| n | 6787 | 502 | 782 | 245 | 133 | | 380 | 234 | 135 | - | 4376 |
| n (ASIAN-HF) | 4687 (69.1%) | 482 (96%) | 656 (83.9%) | 203 (82.9%) | 115 (86.5%) | <0.0001 | 320 (84.2%) | 189 (80.8%) | 118 (87.4%) | <0.0001 | 2604 (59.5%) |
| Sex (Male) | 5271 (77.7%) | 376 (74.9%) | 615 (78.6%) | 192 (78.4%) | 101 (75.9%) | 0.43 | 290 (76.3%) | 174 (74.4%) | 98 (72.6%) | 0.84 | 3425 (78.3%) |
| Age (years) | 62.6 (13.16) | 63.9 (13.13) | 63.9 (13.49) | 61.3 (14.37) | 60.4 (13.85) | 0.001 | 63.4 (13.85) | 62.4 (12.82) | 59.7 (14.23) | 0.002 | 62.3 (12.9) |
| Former smoker | 2504 (36.9%) | 146 (29.1%) | 265 (33.9%) | 101 (41.2%) | 53 (39.8%) | 0.001 | 131 (34.5%) | 78 (33.3%) | 32 (23.7%) | 0.14 | 1698 (38.8%) |
| Current smoker | 913 (13.5%) | 44 (8.8%) | 103 (13.2%) | 21 (8.6%) | 17 (12.8%) | | 42 (11.1%) | 23 (9.8%) | 13 (9.6%) | | 650 (14.9%) |
| Chronic obstructive pulmonary disease | 726 (10.7%) | 68 (13.7%) | 81 (10.4%) | 27 (11%) | 12 (9%) | 0.25 | 52 (13.7%) | 39 (16.7%) | 18 (13.3%) | 0.69 | 429 (9.8%) |
| Myocardial infarction | 2211 (48.1%) | 151 (53.9%) | 275 (54.3%) | 82 (56.6%) | 50 (59.5%) | 0.79 | 123 (53%) | 69 (52.3%) | 40 (59.7%) | 0.77 | 1421 (45.1%) |
| Ischaemic aetiology | 3343 (51.4%) | 226 (50.1%) | 417 (56.3%) | 115 (50%) | 69 (56.1%) | 0.12 | 199 (55.6%) | 115 (50.7%) | 60 (48.4%) | 0.35 | 2142 (50.5%) |
| NYHA Class III/IV | 2691 (42.7%) | 193 (50%) | 352 (50.1%) | 106 (45.7%) | 50 (41%) | 0.2 | 158 (45.9%) | 89 (40.6%) | 45 (35.7%) | 0.018 | 1698 (40.8%) |
| Peripheral oedema | 2058 (30.4%) | 122 (24.6%) | 216 (27.6%) | 68 (27.8%) | 37 (27.8%) | 0.64 | 128 (33.7%) | 73 (31.2%) | 44 (32.6%) | 0.02 | 1370 (31.3%) |
| Orthopnea | 1664 (24.5%) | 140 (28.1%) | 210 (26.9%) | 56 (22.9%) | 37 (27.8%) | 0.49 | 102 (26.8%) | 58 (24.8%) | 36 (26.7%) | 0.83 | 1025 (23.4%) |
| Pulmonary rales | 951 (16.7%) | 76 (15.5%) | 116 (15.9%) | 35 (15.2%) | 20 (15.9%) | 1 | 79 (21.9%) | 50 (23.9%) | 31 (25%) | 0.013 | 544 (15.9%) |
| Previous HF-hospitalization in past year | 2247 (48.8%) | 184 (66.4%) | 327 (60.2%) | 99 (57.6%) | 57 (60.6%) | 0.22 | 131 (60.4%) | 64 (47.8%) | 42 (47.7%) | <0.0001 | 1343 (43.5%) |
| Atrial Fibrillation | 1765 (26%) | 102 (20.5%) | 197 (25.2%) | 80 (32.7%) | 33 (24.8%) | 0.004 | 87 (22.9%) | 38 (16.2%) | 15 (11.1%) | 0.013 | 1213 (27.7%) |
| Diabetes mellitus | 2607 (38.4%) | 199 (40%) | 339 (43.4%) | 94 (38.4%) | 67 (50.4%) | 0.09 | 149 (39.2%) | 90 (38.5%) | 59 (43.7%) | 0.78 | 1610 (36.8%) |
| Hypertension | 3708 (54.7%) | 273 (54.8%) | 429 (54.9%) | 145 (59.2%) | 80 (60.2%) | 0.45 | 163 (42.9%) | 99 (42.3%) | 63 (46.7%) | 0.001 | 2456 (56.2%) |
| Body mass index (kg/m²) | 25.9 (5.4) | 24.3 (4.73) | 24.6 (4.96) | 25.8 (5.33) | 25.2 (4.97) | 0.001 | 24.5 (4.92) | 25.5 (5.11) | 26.5 (7.45) | <0.0001 | 26.4 (5.44) |
| Heart rate (beats/min) | 79.6 (17.26) | 82.8 (18.17) | 78.5 (16.72) | 78.3 (16.01) | 80 (17.28) | 0.004 | 82 (18.46) | 82.1 (18.48) | 81.9 (18.69) | 0.55 | 79.1 (17.03) |
| Systolic blood pressure (mmHg) | 120 (20.58) | 118.1 (21.1) | 116.4 (18.45) | 120.9 (21.3) | 121.4 (21.38) | 0.028 | 115.4 (19.46) | 119.3 (19) | 119.6 (20.66) | 0.33 | 121.1 (20.86) |
| Diastolic blood pressure (mmHg) | 73.1 (12.74) | 72.5 (12.72) | 70.5 (11.7) | 73.3 (12.15) | 73.8 (13.44) | 0.21 | 70.2 (12.01) | 72.5 (11.77) | 73.8 (12.6) | 0.41 | 73.8 (12.96) |
| LVEF (%) | 27.7 (7.21) | 28.2 (7.02) | 27.9 (7.14) | 28 (6.93) | 28.5 (6.9) | 0.97 | 27.4 (7.04) | 28.2 (6.61) | 28.3 (6.55) | 0.94 | 27.5 (7.33) |

| | | | | | | | | | | | |
|-----------------------------------|------------------|-------------------|-------------------|-------------------|---------------------|------|------------------|------------------|--------------------|---------|------------------|
| NT-proBNP (ng/L) | 3641 (1720-8103) | 5410 (2178-11721) | 5300 (2009-16530) | 4295 (1806-10279) | 4663.8 (1947-11059) | 0.64 | 3278 (1987-6980) | 3282 (1567-7729) | 1997.5 (1235-4910) | 0.035 | 3366 (1631-7086) |
| eGFR (ml/min/1.73m ²) | 68.2 (28.64) | 58.2 (28.88) | 59.7 (30.59) | 60.5 (29.39) | 59.4 (30.15) | 0.44 | 66.6 (28.68) | 72 (27.77) | 71.3 (23.83) | <0.0001 | 71.3 (27.63) |

A0=ACEi/ARB 0%; A1=ACEi/ARB 1-49%;

A2=ACEi/ARB 50-99%;

A3=ACEi/ARB ≥100%

B0=BB 0%; B1=BB 1-49%; B2=BB 50-99%; B3=BB ≥100%

p=statistical differences between the subgroups

Table 2: Hazard ratio (95% confidence interval) of patients achieving specific target dose for Mortality or HF-hospitalization, Mortality and HF-hospitalization

| | Mortality or HF-hospitalization | | | |
|------------------------|--|--------------------------|--------------------------|--------------------------|
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | 1.00 (reference) | 0.98 (0.83-1.17; 0.85) | 0.90 (0.71-1.15; 0.41) | 0.68 (0.49-0.93; 0.02) |
| 1-49% ACEi/ARB | 0.90 (0.73-1.10; 0.30) | 0.71 (0.61-0.84; <0.001) | 0.61 (0.49-0.75; <0.001) | 0.80 (0.62-1.04; 0.10) |
| 50-99% ACEi/ARB | 0.67 (0.52-0.87; 0.002) | 0.50 (0.42-0.61; <0.001) | 0.64 (0.54-0.75; <0.001) | 0.57 (0.48-0.68; <0.001) |
| 100% ACEi/ARB | 0.71 (0.52-0.96; 0.03) | 0.52 (0.42-0.64; <0.001) | 0.66 (0.56-0.77; <0.001) | 0.32 (0.26-0.39; <0.001) |
| | Mortality | | | |
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | 1.00 (reference) | 0.75 (0.60-0.92; 0.006) | 0.65 (0.48-0.87; 0.004) | 0.40 (0.25-0.63; <0.001) |
| 1-49% ACEi/ARB | 0.74 (0.57-0.95; 0.02) | 0.57 (0.47-0.69; <0.001) | 0.39 (0.29-0.51; <0.001) | 0.58 (0.42-0.81; 0.001) |
| 50-99% ACEi/ARB | 0.57 (0.42-0.78; <0.001) | 0.33 (0.26-0.42; <0.001) | 0.42 (0.34-0.51; <0.001) | 0.27 (0.21-0.34; <0.001) |
| 100% ACEi/ARB | 0.75 (0.53-1.07; 0.11) | 0.40 (0.30-0.52; <0.001) | 0.38 (0.31-0.46; <0.001) | 0.19 (0.14-0.24; <0.001) |
| | HF-hospitalization | | | |
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | 1.00 (reference) | 1.42 (1.14-1.77; 0.002) | 1.48 (1.12-1.95; 0.006) | 1.10 (0.76-1.59; 0.62) |
| 1-49% ACEi/ARB | 1.26 (0.97-1.63; 0.08) | 1.08 (0.88-1.33; 0.43) | 0.94 (0.72-1.21; 0.64) | 1.14 (0.83-1.57; 0.41) |
| 50-99% ACEi/ARB | 0.80 (0.57-1.11; 0.18) | 0.75 (0.59-0.95; 0.02) | 0.93 (0.76-1.14; 0.50) | 1.14 (0.92-1.41; 0.22) |
| 100% ACEi/ARB | 0.71 (0.46-1.09; 0.12) | 0.81 (0.62-1.05; 0.12) | 1.14 (0.93-1.40; 0.20) | 0.85 (0.68-1.06; 0.17) |

Table S1: Variables used in inverse probability weighting

| Variable | Summary | Percentage missing |
|--|--------------|--------------------|
| n | 6787 | 11 % |
| ASIAN-HF | 4687 (69.1%) | 0 % |
| East Asia | 1544 (22.7%) | 0 % |
| South Asia | 1314 (19.4%) | |
| South-East Asia | 1829 (26.9%) | |
| North EU | 950 (14%) | |
| South EU | 1150 (16.9%) | |
| Country (China) | 440 (6.5%) | 0 % |
| Country (Hong Kong) | 50 (0.7%) | |
| Country (India) | 1314 (19.4%) | |
| Country (Indonesia) | 158 (2.3%) | |
| Country (Japan) | 527 (7.8%) | |
| Country (Korea) | 272 (4%) | |
| Country (Malaysia) | 490 (7.2%) | |
| Country (Philippines) | 24 (0.4%) | |
| Country (Singapore) | 1030 (15.2%) | |
| Country (Taiwan) | 255 (3.8%) | |
| Country (Thailand) | 127 (1.9%) | |
| Country (Netherlands) | 276 (4.1%) | |
| Country (Germany) | 84 (1.2%) | |
| Country (France) | 195 (2.9%) | |
| Country (Greece) | 278 (4.1%) | |
| Country (Italy) | 289 (4.3%) | |
| Country (Norway) | 93 (1.4%) | |
| Country (Poland) | 244 (3.6%) | |
| Country (Serbia) | 366 (5.4%) | |
| Country (Slovenia) | 22 (0.3%) | |
| Country (Sweden) | 96 (1.4%) | |
| Country (UK) | 157 (2.3%) | |
| Age (years) | 62.6 (13.16) | 0 % |
| Sex (Male) | 5271 (77.7%) | 0 % |
| Race (Caucasian) | 2078 (30.6%) | 0 % |
| Race (Chinese) | 1475 (21.7%) | |
| Race (Indians) | 1505 (22.2%) | |
| Race (Malay) | 651 (9.6%) | |
| Race (Japanese) | 528 (7.8%) | |
| Race (Korean) | 272 (4%) | |
| Race (Thai) | 127 (1.9%) | |
| Race (Filipino) | 9 (0.1%) | |
| Race (Indigenous SEA) | 106 (1.6%) | |
| Race (Other) | 33 (0.5%) | |
| NYHA class 1 | 633 (10.1%) | 7 % |
| NYHA class 2 | 2972 (47.2%) | |
| NYHA class 3 | 2199 (34.9%) | |
| NYHA class 4 | 492 (7.8%) | |
| Orthopnea present | 1664 (24.5%) | 0 % |
| Height (m) | 166.4 (9.54) | 3 % |
| Weight (kg) | 72.2 (18.11) | 3 % |
| BMI (kg/m ²) | 25.9 (5.4) | 3 % |
| Heart rate (beats/min) | 79.6 (17.26) | 1 % |
| Systolic blood pressure (mmHg) | 120 (20.58) | 0 % |
| Diastolic blood pressure (mmHg) | 73.1 (12.74) | 0 % |
| jugular venous pressure | 1132 (18.6%) | 10 % |
| Peripheral oedema | 2058 (30.4%) | 0 % |
| Rales | 951 (16.7%) | 16 % |
| Hepatomegaly | 542 (8%) | 0 % |
| Ischemic aetiology | 3343 (51.4%) | 4 % |
| Previous hospitalization for heart failure | 2247 (48.8%) | 32 % |
| Device therapy (ICD only) | 368 (5.4%) | 0 % |
| Device therapy (Pacemaker only) | 260 (3.8%) | |
| Device therapy (Biventricular Pacer only) | 124 (1.8%) | |
| Device therapy (Biventricular Pacer and ICD) | 464 (6.9%) | |
| Coronary artery disease | 3336 (49.2%) | 0 % |
| Myocardial infarction | 2211 (48.1%) | 32 % |
| Percutaneous coronary intervention | 1390 (30.3%) | 32 % |
| Valvular surgery | 717 (15.6%) | 32 % |
| Atrial Fibrillation | 1765 (26%) | 0 % |

| | | |
|---------------------------------------|-----------------|------|
| Hypertension | 3708 (54.7%) | 0 % |
| Stroke | 502 (7.4%) | 0 % |
| Peripheral artery disease | 378 (5.6%) | 0 % |
| Chronic obstructive pulmonary disease | 726 (10.7%) | 0 % |
| Diabetes mellitus | 2607 (38.4%) | 0 % |
| Smoking (Ever) | 2504 (36.9%) | 0 % |
| Smoking (Never) | 913 (13.5%) | |
| Alcohol history | 1139 (16.8%) | 0 % |
| Serum Creatinine (μmol/L) | 4.7 (0.44) | 14 % |
| Estimated GFR, calculated with MDRD | 68.2 (28.64) | 15 % |
| Sodium (mmol/L) | 138.6 (4.03) | 20 % |
| Potassium (mmol/L) | 4.3 (0.56) | 17 % |
| Haemoglobin (g/dL) | 13.2 (2.01) | 20 % |
| Blood Urea Nitrogen (mmol/L) | 10.3 (8.78) | 33 % |
| log-NT-proBNP (ng/L) | 8.2 (7.45-9) | 68 % |
| log-BNP (ng/L) | 6.3 (5.23-7.28) | 85 % |
| LVEF (%) | 28 (22-34) | 3 % |

Table S2: Baseline characteristics for ASIAN-HF and BIOSTAT-CHF cohorts

| Variable | ASIAN-HF | BIOSTAT-CHF | p value | excluded ASIAN-HF | excluded BIOSTAT-CHF |
|--|------------------|------------------|---------|-------------------|----------------------|
| n | 4687 | 2100 | | 589 | 416 |
| Sex (Male) | 3682 (78.6%) | 1589 (75.7%) | 0.008 | 441 (74.9%) | 257 (61.8%) |
| Age (years) | 60.3 (13.03) | 67.7 (11.95) | <0.0001 | 58.7 (13.19) | 75 (9.97) |
| Ischaemic aetiology | 2189 (49.8%) | 1154 (55%) | 0.0001 | 281 (51.5%) | 204 (49%) |
| NYHA Class III/IV | 1455 (34.3%) | 1236 (60.3%) | <0.0001 | 213 (39.6%) | 286 (72.2%) |
| peripheral oedema | 1070 (22.9%) | 988 (47%) | <0.0001 | 171 (30.1%) | 268 (64.4%) |
| Orthopnea | 986 (21.1%) | 678 (32.3%) | <0.0001 | 200 (35.1%) | 201 (48.6%) |
| pulmonary rales | 768 (16.4%) | 183 (18%) | 0.22 | 111 (19.5%) | 65 (23.8%) |
| Previous HF-hospitalization in past year | 1578 (62.9%) | 669 (31.9%) | <0.0001 | 193 (65%) | 125 (30%) |
| Atrial Fibrillation | 864 (18.5%) | 901 (42.9%) | <0.0001 | 77 (13.6%) | 242 (58.2%) |
| Diabetes mellitus | 1931 (41.2%) | 676 (32.2%) | <0.0001 | 189 (33.3%) | 143 (34.4%) |
| Hypertension | 2431 (51.9%) | 1277 (60.8%) | <0.0001 | 288 (50.8%) | 292 (70.2%) |
| Body mass index (kg/m ²) | 24.9 (5.06) | 28 (5.52) | <0.0001 | 24.6 (5.51) | 27.4 (5.34) |
| Heart rate (beats/min) | 79.5 (16.19) | 79.8 (19.43) | 0.51 | 80.9 (15.84) | 80.8 (19.71) |
| Systolic blood pressure (mmHg) | 118.1 (19.99) | 124.2 (21.24) | <0.0001 | 121.1 (20.03) | 127.3 (24.85) |
| Diastolic blood pressure (mmHg) | 72 (12.45) | 75.5 (13.05) | <0.0001 | 75.2 (13.19) | 71.9 (14.52) |
| LVEF (%) | 27.3 (7.06) | 28.6 (7.49) | <0.0001 | 28.1 (22-34) | 45 (35-55) |
| NT-proBNP (ng/L) | 3294 (1436-8103) | 4024 (2253-8185) | <0.0001 | 4023 (1339-11849) | 4495 (2713-9000) |
| eGFR (ml/min/1.73m ²) | 66.1 (27.85) | 71.9 (29.65) | <0.0001 | 63 (27.11) | 64.2 (28.79) |
| Combined Endpoint | 1441 (31%) | 741 (35%) | | | |
| All-cause mortality | 864 (18%) | 423 (20%) | | | |
| Heart failure hospitalization | 1119 (24%) | 500 (24%) | | | |

Table S3: Baseline characteristics of groups achieving 0%, 1-49%, 50-99% and 100% guideline recommended target doses for ACE-inhibitor/ARB and beta-blocker

| Variable | All | A0B0 | A0B1 | A0B2 | A0B3 | A1B0 | A1B1 | A1B2 | A1B3 |
|---|------------------|-------------------|-------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|
| n | 6787 | 502 | 782 | 245 | 133 | 380 | 1524 | 458 | 185 |
| n (ASIAN-HF) | 4687 (69.1%) | 482 (96%) | 656 (83.9%) | 203 (82.9%) | 115 (86.5%) | 320 (84.2%) | 1049 (68.8%) | 305 (66.6%) | 134 (72.4%) |
| Sex (Male) | 5271 (77.7%) | 376 (74.9%) | 615 (78.6%) | 192 (78.4%) | 101 (75.9%) | 290 (76.3%) | 1188 (78%) | 366 (79.9%) | 151 (81.6%) |
| Age (years) | 62.6 (13.16) | 63.9 (13.13) | 63.9 (13.49) | 61.3 (14.37) | 60.4 (13.85) | 63.4 (13.85) | 62.1 (12.95) | 62.3 (12.59) | 61.5 (12.49) |
| Former smoker | 2504 (36.9%) | 146 (29.1%) | 265 (33.9%) | 101 (41.2%) | 53 (39.8%) | 131 (34.5%) | 567 (37.2%) | 156 (34.1%) | 86 (46.5%) |
| Current smoker | 913 (13.5%) | 44 (8.8%) | 103 (13.2%) | 21 (8.6%) | 17 (12.8%) | 42 (11.1%) | 257 (16.9%) | 71 (15.5%) | 23 (12.4%) |
| Chronic obstructive pulmonary disease | 726 (10.7%) | 68 (13.7%) | 81 (10.4%) | 27 (11%) | 12 (9%) | 52 (13.7%) | 154 (10.1%) | 47 (10.3%) | 13 (7%) |
| Myocardial infarction | 2211 (48.1%) | 151 (53.9%) | 275 (54.3%) | 82 (56.6%) | 50 (59.5%) | 123 (53%) | 492 (46.9%) | 139 (45.3%) | 61 (47.3%) |
| Ischaemic aetiology | 3343 (51.4%) | 226 (50.1%) | 417 (56.3%) | 115 (50%) | 69 (56.1%) | 199 (55.6%) | 740 (50.4%) | 219 (49.5%) | 93 (52.8%) |
| NYHA Class III/IV | 2691 (42.7%) | 193 (50%) | 352 (50.1%) | 106 (45.7%) | 50 (41%) | 158 (45.9%) | 571 (40.2%) | 157 (36%) | 53 (29.8%) |
| Peripheral oedema | 2058 (30.4%) | 122 (24.6%) | 216 (27.6%) | 68 (27.8%) | 37 (27.8%) | 128 (33.7%) | 463 (30.4%) | 135 (29.5%) | 58 (31.4%) |
| Orthopnea | 1664 (24.5%) | 140 (28.1%) | 210 (26.9%) | 56 (22.9%) | 37 (27.8%) | 102 (26.8%) | 348 (22.9%) | 101 (22.1%) | 42 (22.7%) |
| Pulmonary rales | 951 (16.7%) | 76 (15.5%) | 116 (15.9%) | 35 (15.2%) | 20 (15.9%) | 79 (21.9%) | 222 (17.1%) | 51 (13.5%) | 17 (11%) |
| Previous HF-hospitalization in past year | 2247 (48.8%) | 184 (66.4%) | 327 (60.2%) | 99 (57.6%) | 57 (60.6%) | 131 (60.4%) | 470 (49%) | 141 (45.2%) | 73 (55.3%) |
| Atrial Fibrillation | 1765 (26%) | 102 (20.5%) | 197 (25.2%) | 80 (32.7%) | 33 (24.8%) | 87 (22.9%) | 403 (26.5%) | 148 (32.3%) | 74 (40%) |
| Diabetes mellitus | 2607 (38.4%) | 199 (40%) | 339 (43.4%) | 94 (38.4%) | 67 (50.4%) | 149 (39.2%) | 539 (35.4%) | 177 (38.6%) | 82 (44.3%) |
| Hypertension | 3708 (54.7%) | 273 (54.8%) | 429 (54.9%) | 145 (59.2%) | 80 (60.2%) | 163 (42.9%) | 740 (48.6%) | 239 (52.2%) | 112 (60.5%) |
| Body mass index (kg/m^2) | 25.9 (5.4) | 24.3 (4.73) | 24.6 (4.96) | 25.8 (5.33) | 25.2 (4.97) | 24.5 (4.92) | 25.3 (5.02) | 25.9 (4.91) | 26.4 (5.34) |
| Heart rate (beats/min) | 79.6 (17.26) | 82.8 (18.17) | 78.5 (16.72) | 78.3 (16.01) | 80 (17.28) | 82 (18.46) | 78.5 (16.51) | 78.8 (15.9) | 80.9 (18.27) |
| Systolic blood pressure (mmHg) | 120 (20.58) | 118.1 (21.1) | 116.4 (18.45) | 120.9 (21.3) | 121.4 (21.38) | 115.4 (19.46) | 115.8 (18.71) | 118.3 (20.28) | 119.8 (19.2) |
| Diastolic blood pressure (mmHg) | 73.1 (12.74) | 72.5 (12.72) | 70.5 (11.7) | 73.3 (12.15) | 73.8 (13.44) | 70.2 (12.01) | 70.5 (11.95) | 72.6 (12.78) | 71.7 (12.83) |
| LVEF (%) | 27.7 (7.21) | 28.2 (7.02) | 27.9 (7.14) | 28 (6.93) | 28.5 (6.9) | 27.4 (7.04) | 26.6 (7.37) | 27.2 (7.36) | 27.6 (7.25) |
| NT-proBNP (ng/L) | 3641 (1720-8103) | 5410 (2178-11721) | 5300 (2008-16530) | 4295 (1806-10279) | 4664 (1947-11059) | 3278 (1987-6980) | 3236 (1480-7114) | 3009 (1598-7083) | 3510 (2271-7616) |
| eGFR (ml/min/1.73m^2) | 68.2 (28.64) | 58.2 (28.88) | 59.7 (30.59) | 60.5 (29.39) | 59.4 (30.15) | 66.6 (28.68) | 70.8 (27.43) | 69.4 (28.78) | 62.9 (27.16) |
| Potassium (mmol/L) | 6787 | 4.2 (0.64) | 4.3 (0.55) | 4.3 (0.56) | 4.3 (0.57) | 4.2 (0.53) | 4.2 (0.54) | 4.3 (0.57) | 4.2 (0.52) |
| MRA use at baseline | | 173 (34%) | 410 (52%) | 146 (60%) | 77 (58%) | 214 (56%) | 952 (62%) | 280 (61%) | 109 (59%) |

A0=ACEi/ARB 0%; A1=ACEi/ARB 1-49%; A2=ACEi/ARB 50-99%; A3=ACEi/ARB ≥100%

B0=BB 0%; B1=BB 1-49%; B2=BB 50-99%; B3=BB ≥100%

| Variable | A2B0 | A2B1 | A2B2 | A2B3 | A3B0 | A3B1 | A3B2 | A3B3 | p |
|---|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|---------|
| n | 234 | 797 | 340 | 178 | 135 | 431 | 273 | 190 | |
| n (ASIAN-HF) | 189 (80.8%) | 428 (53.7%) | 160 (47.1%) | 109 (61.2%) | 118 (87.4%) | 201 (46.6%) | 120 (44%) | 98 (51.6%) | <0.0001 |
| Sex (Male) | 174 (74.4%) | 619 (77.7%) | 268 (78.8%) | 135 (75.8%) | 98 (72.6%) | 334 (77.5%) | 219 (80.2%) | 145 (76.3%) | 0.7 |
| Age (years) | 62.4 (12.82) | 63.1 (12.73) | 61.9 (13.09) | 59.7 (14.27) | 59.7 (14.23) | 64.6 (12.47) | 62.2 (12.26) | 59.9 (13.71) | <0.0001 |
| Former smoker | 78 (33.3%) | 292 (36.6%) | 155 (45.6%) | 80 (44.9%) | 32 (23.7%) | 170 (39.4%) | 112 (41%) | 80 (42.1%) | <0.0001 |
| Current smoker | 23 (9.8%) | 110 (13.8%) | 50 (14.7%) | 22 (12.4%) | 13 (9.6%) | 53 (12.3%) | 40 (14.7%) | 24 (12.6%) | |
| Chronic obstructive pulmonary disease | 39 (16.7%) | 84 (10.5%) | 31 (9.1%) | 14 (7.9%) | 18 (13.3%) | 41 (9.5%) | 28 (10.3%) | 17 (8.9%) | 0.047 |
| Myocardial infarction | 69 (52.3%) | 264 (44.7%) | 123 (45.4%) | 58 (49.2%) | 40 (59.7%) | 143 (42.1%) | 89 (42.2%) | 52 (38%) | 0.0001 |
| Ischaemic aetiology | 115 (50.7%) | 395 (50.3%) | 185 (55.7%) | 88 (51.5%) | 60 (48.4%) | 217 (51.3%) | 129 (48.9%) | 76 (41.3%) | 0.07 |
| NYHA Class III/IV | 89 (40.6%) | 340 (44.4%) | 134 (41.2%) | 65 (38%) | 45 (35.7%) | 191 (45.6%) | 117 (44.2%) | 70 (37.6%) | <0.0001 |
| Peripheral oedema | 73 (31.2%) | 242 (30.4%) | 117 (34.4%) | 48 (27%) | 44 (32.6%) | 152 (35.3%) | 96 (35.2%) | 59 (31.1%) | 0.039 |
| Orthopnea | 58 (24.8%) | 205 (25.7%) | 77 (22.6%) | 39 (21.9%) | 36 (26.7%) | 114 (26.5%) | 61 (22.3%) | 38 (20%) | 0.27 |
| Pulmonary rales | 50 (23.9%) | 104 (17.5%) | 35 (15.2%) | 18 (12.7%) | 31 (25%) | 56 (17.8%) | 28 (15.2%) | 13 (9.8%) | 0.002 |
| Previous HF-hospitalization in past year | 64 (47.8%) | 244 (40.8%) | 104 (40.8%) | 60 (44.8%) | 42 (47.7%) | 104 (32.2%) | 83 (37.6%) | 64 (42.7%) | <0.0001 |
| Atrial Fibrillation | 38 (16.2%) | 180 (22.6%) | 93 (27.4%) | 57 (32%) | 15 (11.1%) | 111 (25.8%) | 88 (32.2%) | 59 (31.1%) | <0.0001 |
| Diabetes mellitus | 90 (38.5%) | 282 (35.4%) | 118 (34.7%) | 75 (42.1%) | 59 (43.7%) | 167 (38.7%) | 95 (34.8%) | 75 (39.5%) | 0.003 |
| Hypertension | 99 (42.3%) | 464 (58.3%) | 203 (59.7%) | 112 (62.9%) | 63 (46.7%) | 289 (67.1%) | 176 (64.5%) | 121 (63.7%) | <0.0001 |
| Body mass index (kg/m^2) | 25.5 (5.11) | 26.4 (5.01) | 27.6 (6.18) | 27.9 (5.19) | 26.5 (7.45) | 27.3 (5.89) | 28.4 (6.02) | 28.4 (6.15) | <0.0001 |
| Heart rate (beats/min) | 82.1 (18.48) | 78.7 (16.63) | 79.6 (17.23) | 81.9 (19) | 81.9 (18.69) | 78.7 (17.13) | 79.2 (17.92) | 81.8 (19.77) | <0.0001 |
| Systolic blood pressure (mmHg) | 119.3 (19) | 122.1 (20.15) | 125.9 (20.65) | 123.3 (19.4) | 119.6 (20.66) | 128.8 (23.46) | 127.7 (21.89) | 130.5 (23.5) | <0.0001 |
| Diastolic blood pressure (mmHg) | 72.5 (11.77) | 74.6 (12.45) | 76.3 (12.32) | 76.3 (12.25) | 73.8 (12.6) | 77.5 (13.19) | 79.2 (14.68) | 79.5 (13.76) | <0.0001 |
| LVEF (%) | 28.2 (6.61) | 27.8 (7.17) | 27.7 (7.25) | 28.3 (7.37) | 28.3 (6.55) | 29.1 (7.13) | 28 (7.48) | 28.3 (7.22) | <0.0001 |
| NT-proBNP (ng/L) | 3282 (1567-7729) | 3596 (1852-7378) | 3048 (1547-6907) | 4241 (2399-8523) | 1998 (1235-4910) | 3274 (2008-6441) | 3457 (1936-6121) | 2496 (1200-5145) | <0.0001 |
| eGFR (ml/min/1.73m^2) | 72 (27.77) | 72.2 (25.86) | 73.3 (26.06) | 69.7 (28.3) | 71.3 (23.83) | 74 (29.45) | 71.9 (28.5) | 75.6 (28.64) | <0.0001 |
| Potassium (mmol/L) | 4.2 (0.58) | 4.3 (0.56) | 4.3 (0.53) | 4.2 (0.55) | 4.3 (0.62) | 4.3 (0.59) | 4.3 (0.53) | 4.3 (0.49) | 0.4695 |
| MRA use | 124 (53%) | 481 (60%) | 185 (54%) | 97 (54%) | 78 (58%) | 249 (58%) | 160 (59%) | 109 (57%) | <0.001 |

A0=ACEi/ARB 0%; A1=ACEi/ARB 1-49%; A2=ACEi/ARB 50-99%; A3=ACEi/ARB ≥100%

B0=BB 0%; B1=BB 1-49%; B2=BB 50-99%; B3=BB ≥100%

Table S4: Results of multivariate logistic analyses predicting attainment of $\geq 50\%$ GRTD for either ACEi/ARB or β -blockers

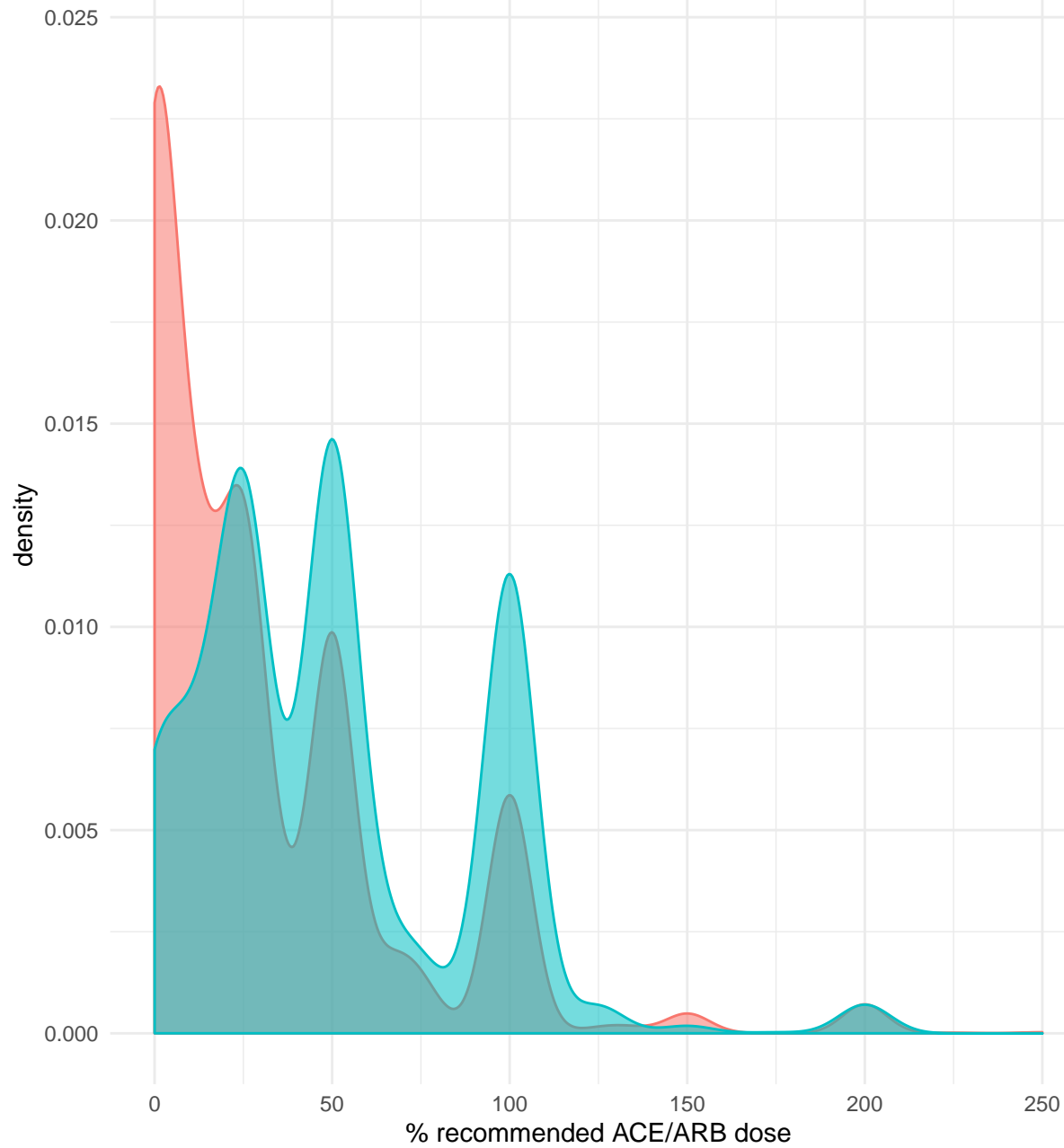
| Variable | OR | 95% CI | p-value |
|---|-------|----------------|---------|
| (Intercept) | 0.00 | (0-30.45) | 0.11 |
| Country (China) | - | - | - |
| Country (Hong Kong) | 12.48 | (3.88-40.10) | <0.0001 |
| Country (India) | 6.78 | (3.07-14.96) | <0.0001 |
| Country (Indonesia) | 11.80 | (4.73-29.46) | <0.0001 |
| Country (Japan) | 3.15 | (1.29-7.69) | 0.01 |
| Country (Korea) | 25.78 | (11.39-58.35) | <0.0001 |
| Country (Malaysia) | 14.21 | (6.33-31.94) | <0.0001 |
| Country (Philippines) | 6.58 | (1.26-34.41) | 0.03 |
| Country (Singapore) | 7.94 | (3.57-17.65) | <0.0001 |
| Country (Taiwan) | 3.94 | (1.55-9.99) | 0.004 |
| Country (Thailand) | 9.10 | (3.51-23.61) | <0.0001 |
| Country (Netherlands) | 32.56 | (14.20-74.63) | <0.0001 |
| Country (Germany) | 25.64 | (10.08-65.22) | <0.0001 |
| Country (France) | 39.42 | (17.09-90.89) | <0.0001 |
| Country (Greece) | 3.23 | (1.27-8.22) | 0.01 |
| Country (Italy) | 15.82 | (6.81-36.78) | <0.0001 |
| Country (Norway) | 37.68 | (15.33-92.61) | <0.0001 |
| Country (Poland) | 17.24 | (7.44-39.96) | <0.0001 |
| Country (Serbia) | 12.72 | (5.62-28.78) | <0.0001 |
| Country (Slovenia) | 31.65 | (9.70-103.22) | <0.0001 |
| Country (Sweden) | 71.73 | (29.56-174.05) | <0.0001 |
| Country (UK) | 8.82 | (3.46-22.50) | <0.0001 |
| Age (years) | 0.98 | (0.97-0.99) | <0.0001 |
| Sex (male) | 1.06 | (0.83-1.35) | 0.63 |
| LVEF (%) | 1.00 | (0.99-1.01) | 0.65 |
| HF-hospitalization in year before inclusion | 0.87 | (0.71-1.06) | 0.16 |
| Orthopnea present | 0.83 | (0.67-1.03) | 0.1 |
| Height (m) | 1.01 | (0.98-1.04) | 0.52 |
| Weight (kg) | 1.01 | (0.98-1.04) | 0.56 |
| Body mass index (kg/m ²) | 1.02 | (0.94-1.11) | 0.64 |

| | | | |
|---------------------------------------|------|-------------|---------|
| Rales | 0.91 | (0.72-1.16) | 0.46 |
| Ischemic aetiology | 0.90 | (0.74-1.08) | 0.26 |
| Percutaneous coronary intervention | 1.14 | (0.95-1.38) | 0.17 |
| Alcohol usage | 1.02 | (0.83-1.25) | 0.84 |
| NYHA class I | - | - | - |
| NYHA class II | 0.83 | (0.64-1.08) | 0.16 |
| NYHA class III | 0.83 | (0.62-1.11) | 0.2 |
| NYHA class IV | 0.58 | (0.37-0.91) | 0.02 |
| Myocardial infarction | 1.21 | (1.00-1.47) | 0.048 |
| Heart Rate (bpm) | 1.00 | (0.99-1.00) | 0.27 |
| Systolic blood pressure (mmHg) | 1.01 | (1.00-1.01) | <0.0001 |
| Diastolic blood pressure (mmHg) | 1.01 | (1.00-1.02) | 0.013 |
| Peripheral oedema present | 0.82 | (0.69-0.99) | 0.037 |
| Atrial Fibrillation | 1.09 | (0.91-1.31) | 0.33 |
| Hypertension | 1.31 | (1.11-1.55) | 0.0017 |
| Peripheral Artery Disease | 0.76 | (0.54-1.07) | 0.11 |
| Chronic obstructive pulmonary disease | 0.76 | (0.58-0.98) | 0.03 |
| Smoking (never) | - | - | - |
| Smoking (current) | 1.20 | (1.00-1.43) | 0.0495 |
| Smokin (ever) | 1.00 | (0.78-1.28) | 0.99 |
| log-B-type natriuretic peptide (ng/L) | 0.99 | (0.93-1.04) | 0.59 |
| Hemoglobin (g/dL) | 1.02 | (0.97-1.06) | 0.46 |
| eGFR (ml/min/1.73m2) | 0.99 | (0.99-1.00) | 0.056 |
| serum Creatinine µmol/L | 0.49 | (0.29-0.83) | 0.008 |
| Sodium (mmol/L) | 1.01 | (0.99-1.04) | 0.31 |
| Potassium (mmol/L) | 1.16 | (1.01-1.34) | 0.04 |
| Blood Urea Nitrogen (mmol/L) | 1.00 | (0.98-1.01) | 0.71 |
| log-N-terminal-pro-BNP (ng/L) | 0.96 | (0.89-1.03) | 0.23 |

Table S5: Hazard ratio (95% confidence interval) of patients achieving specific target dose for Mortality or HF-hospitalization, Mortality and HF-hospitalization stratified by sex.

| MEN | Mortality or HF-hospitalization | | | |
|-----------------|---------------------------------|--------------------------|--------------------------|--------------------------|
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | - | 0.94 (0.77-1.15; 0.55) | 0.87 (0.67-1.14; 0.32) | 0.60 (0.41-0.88; 0.01) |
| 1-49% ACEi/ARB | 0.89 (0.71-1.13; 0.35) | 0.74 (0.62-0.89; <0.001) | 0.62 (0.49-0.79; <0.001) | 0.78 (0.58-1.04; 0.09) |
| 50-99% ACEi/ARB | 0.62 (0.46-0.83; 0.002) | 0.51 (0.41-0.63; <0.001) | 0.70 (0.59-0.84; <0.001) | 0.56 (0.46-0.69; <0.001) |
| 100% ACEi/ARB | 0.60 (0.41-0.88; 0.008) | 0.50 (0.39-0.64; <0.001) | 0.63 (0.52-0.75; <0.001) | 0.31 (0.25-0.39; <0.001) |
| | Mortality | | | |
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | - | 0.73 (0.57-0.93; 0.01) | 0.64 (0.45-0.91; 0.01) | 0.37 (0.21-0.63; <0.001) |
| 1-49% ACEi/ARB | 0.75 (0.56-1.00; 0.05) | 0.64 (0.51-0.80; <0.001) | 0.40 (0.30-0.55; <0.001) | 0.63 (0.43-0.91; 0.01) |
| 50-99% ACEi/ARB | 0.56 (0.39-0.81; 0.002) | 0.35 (0.27-0.46; <0.001) | 0.49 (0.40-0.61; <0.001) | 0.29 (0.22-0.38; <0.001) |
| 100% ACEi/ARB | 0.74 (0.49-1.13; 0.16) | 0.42 (0.31-0.57; <0.001) | 0.39 (0.31-0.50; <0.001) | 0.15 (0.11-0.21; <0.001) |
| | HF-hospitalization | | | |
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | - | 1.44 (1.11-1.87; 0.006) | 1.59 (1.14-2.21; 0.006) | 1.16 (0.74-1.82; 0.51) |
| 1-49% ACEi/ARB | 1.39 (1.03-1.88; 0.03) | 1.18 (0.92-1.50; 0.19) | 1.02 (0.76-1.39; 0.88) | 1.22 (0.84-1.78; 0.30) |
| 50-99% ACEi/ARB | 0.82 (0.55-1.23; 0.33) | 0.85 (0.64-1.12; 0.25) | 0.91 (0.65-1.27; 0.57) | 1.11 (0.75-1.65; 0.61) |
| 100% ACEi/ARB | 0.68 (0.4-1.16; 0.15) | 0.88 (0.64-1.21; 0.41) | 1.05 (0.74-1.48; 0.80) | 0.81 (0.53-1.24; 0.33) |
| WOMEN | Mortality or HF-hospitalization | | | |
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | - | 1.11 (0.77-1.61; 0.58) | 1.00 (0.61-1.65; 0.99) | 0.94 (0.51-1.74; 0.84) |
| 1-49% ACEi/ARB | 0.88 (0.56-1.38; 0.59) | 0.59 (0.41-0.84; 0.003) | 0.51 (0.31-0.84; 0.008) | 0.86 (0.47-1.55; 0.61) |
| 50-99% ACEi/ARB | 0.85 (0.51-1.42; 0.54) | 0.47 (0.31-0.71; <0.001) | 0.43 (0.30-0.61; <0.001) | 0.56 (0.39-0.82; 0.003) |
| 100% ACEi/ARB | 1.06 (0.61-1.86; 0.83) | 0.58 (0.37-0.91; 0.02) | 0.77 (0.55-1.09; 0.1416) | 0.35 (0.24-0.53; <0.001) |
| | Mortality | | | |
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | - | 0.79 (0.52-1.20; 0.27) | 0.67 (0.37-1.22; 0.194) | 0.47 (0.21-1.06; 0.07) |
| 1-49% ACEi/ARB | 0.71 (0.43-1.19; 0.19) | 0.34 (0.23-0.52; <0.001) | 0.33 (0.18-0.60; <0.001) | 0.44 (0.20-0.96; 0.04) |
| 50-99% ACEi/ARB | 0.58 (0.32-1.05; 0.07) | 0.28 (0.17-0.45; <0.001) | 0.21 (0.14-0.32; <0.001) | 0.22 (0.14-0.36; <0.001) |
| 100% ACEi/ARB | 0.74 (0.49-1.13; 0.16) | 0.42 (0.31-0.57; <0.001) | 0.39 (0.31-0.50; <0.001) | 0.15 (0.11-0.21; <0.001) |
| | HF-hospitalization | | | |
| | 0% BB | 1-49% BB | 50-99% BB | 100% BB |
| 0% ACEi/ARB | - | 1.68 (1.00-2.82; 0.05) | 1.88 (0.98-3.60; 0.057) | 1.62 (0.72-3.65; 0.25) |
| 1-49% ACEi/ARB | 1.18 (0.62-2.23; 0.62) | 1.34 (0.83-2.18; 0.23) | 1.40 (0.76-2.59; 0.2791) | 1.51 (0.67-3.40; 0.32) |
| 50-99% ACEi/ARB | 1.26 (0.62-2.56; 0.53) | 0.99 (0.57-1.72; 0.97) | 0.88 (0.43-1.83; 0.7355) | 1.63 (0.79-3.39; 0.19) |
| 100% ACEi/ARB | 1.10 (0.47-2.58; 0.83) | 1.34 (0.74-2.44; 0.34) | 1.59 (0.81-3.13; 0.1795) | 0.75 (0.30-1.86; 0.53) |

Figure 1



[Click here to access/download;Figure;Figure 1.pdf](#)

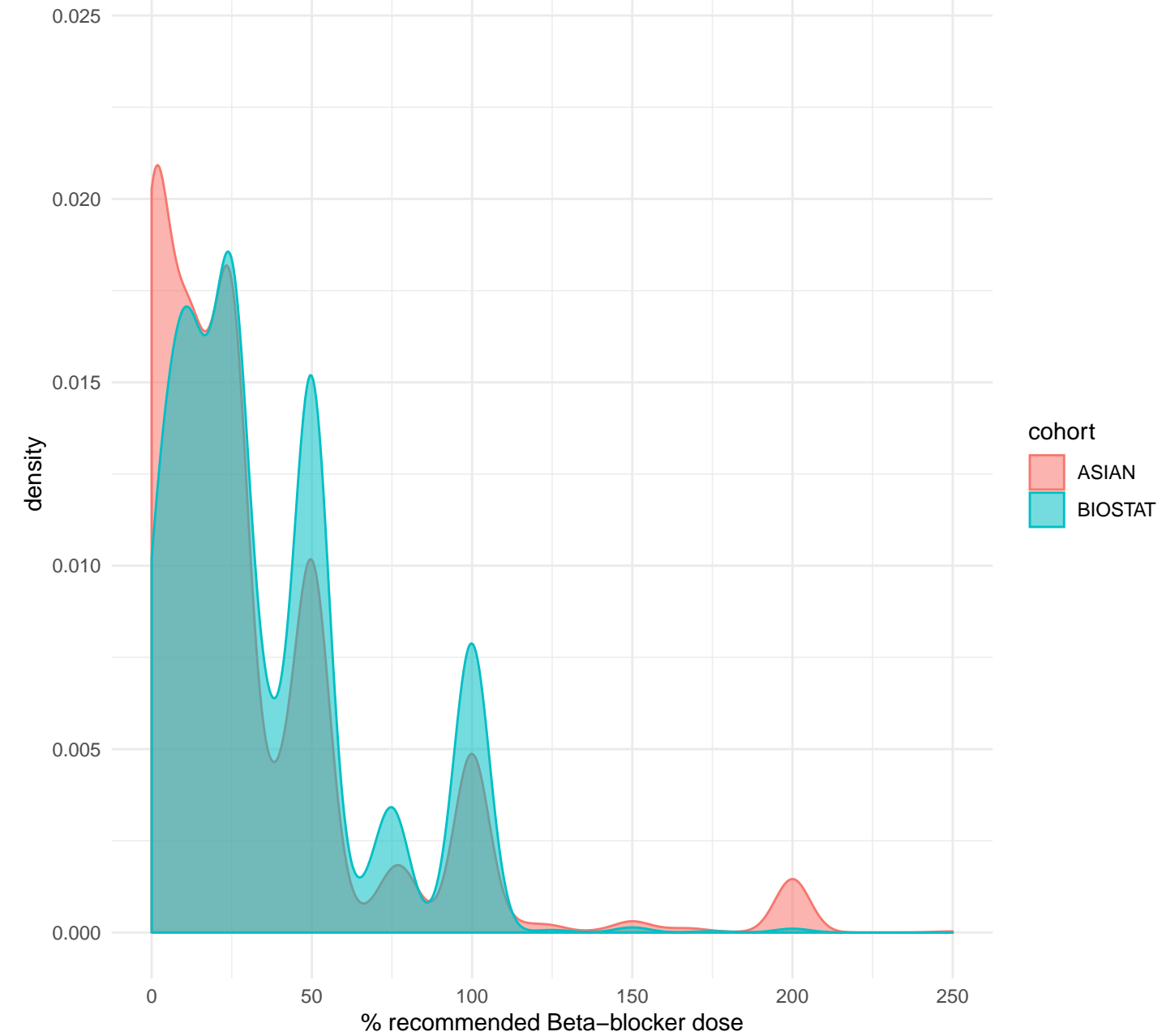


Figure 2a

[Click here to access/download;Figure;Figure 2a.png](#)

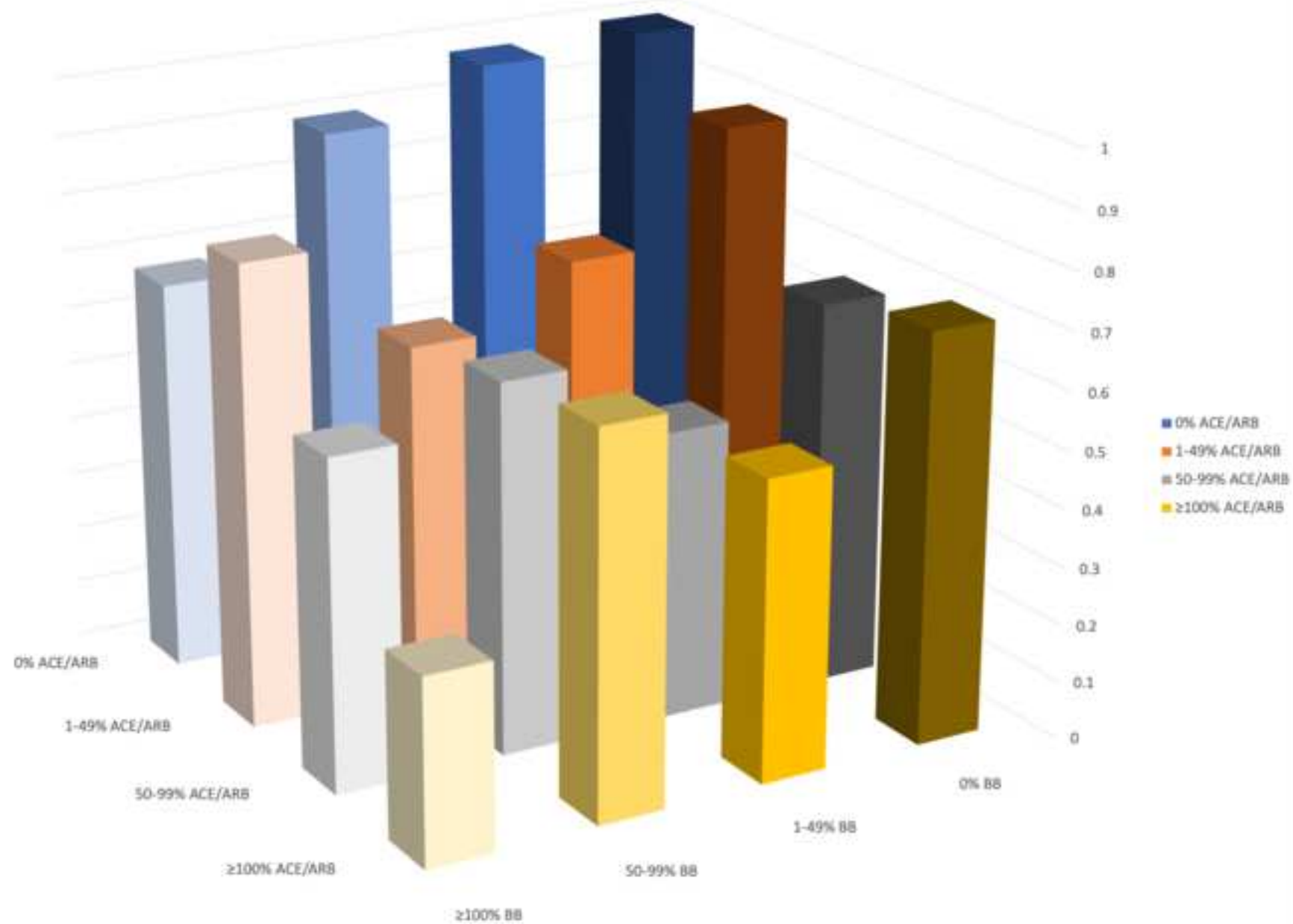
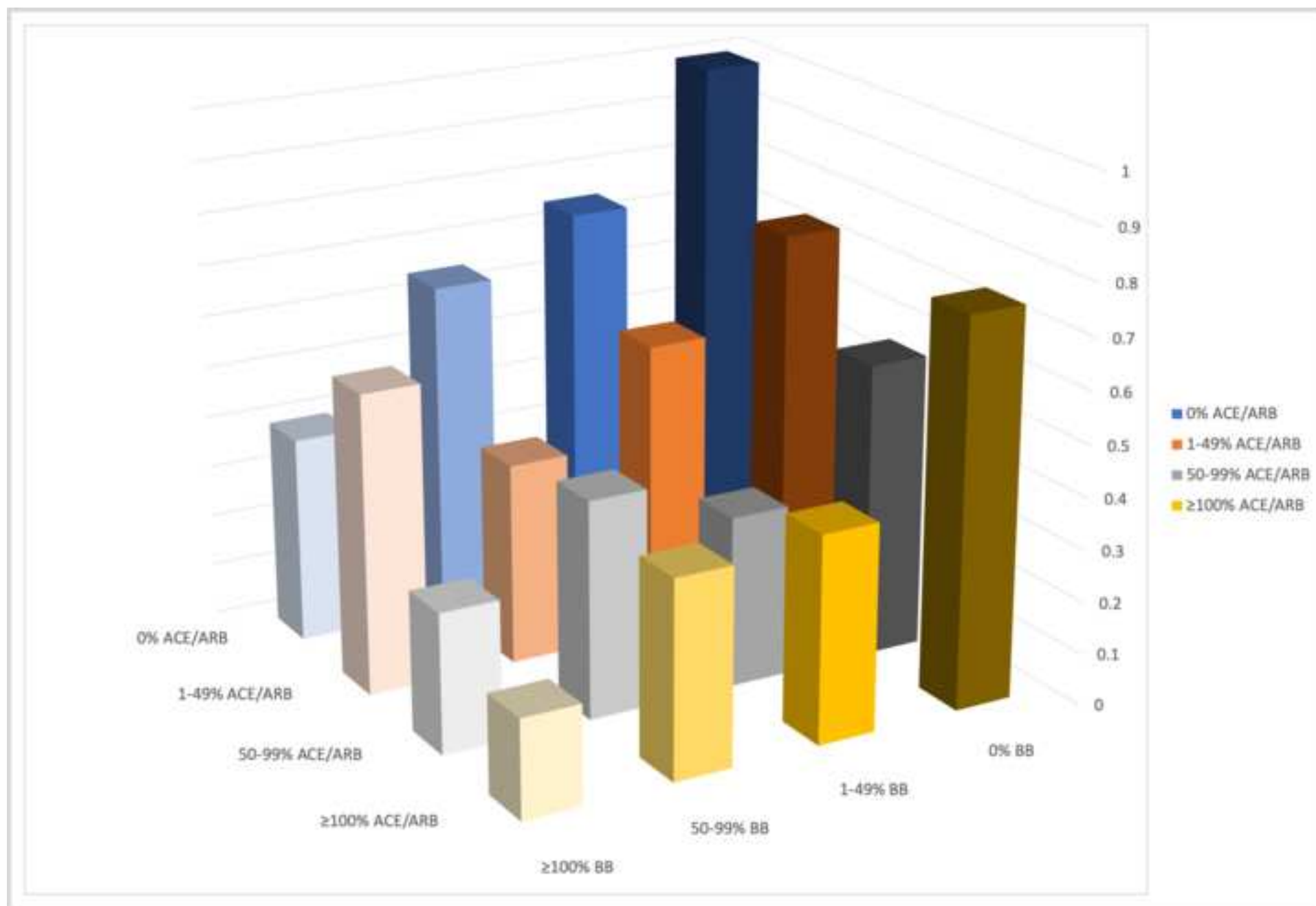
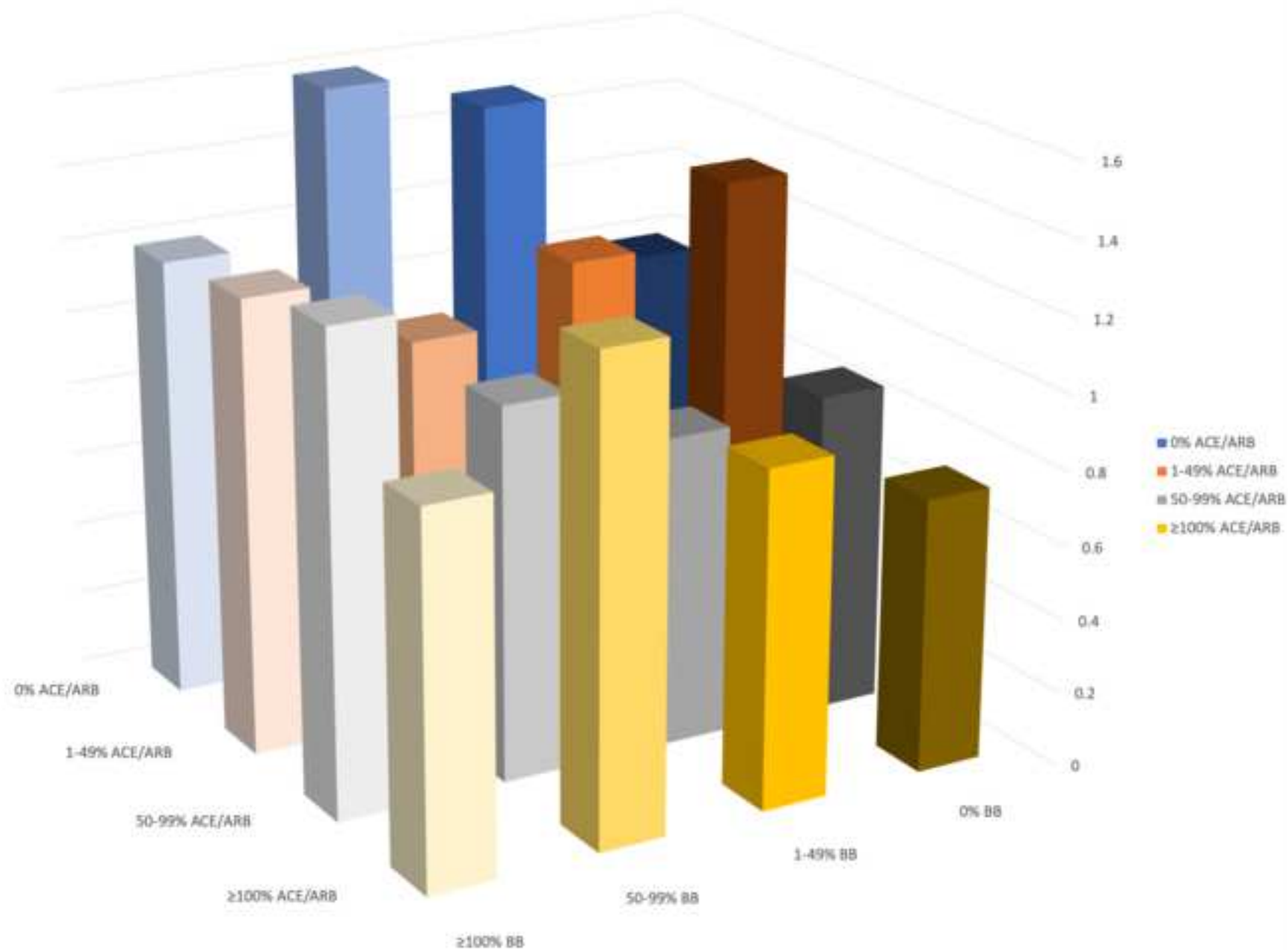



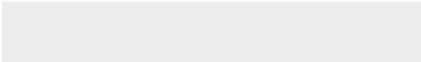

Figure 2b







Click here to access/download
Supplementary Material
Figure S1.pdf



The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission